ARCHIVES OF PATHOLOGY

VOLUME 14 DECEMBER, 1932 NUMBER 6

APPENDICITIS IN MEASLES

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Warthin [1] recently reported the finding of giant cells in the tonsils and pharyngeal mucosa of four patients who were in the prodromal stage of measles. He considered the change in the organs mentioned to be pathognomonic. A cervical lymph node removed from one of the patients showed no such change.

In his review of the literature up to the time of his publication, he referred to an article by Ewing [2] in 1909 and to one by Mallory and Medlar [3] in 1920 on the changes in the skin and mucous membranes in measles. None of these authors noted the occurrence of giant cells in the mucous membranes. Commenting on their findings, Warthin stated:

> In measles either there is a difference in the pathology of the lesion in the mucous membranes of the tonsil and pharynx from that of the buccal mucosa or these investigators missed what is to my mind the most striking feature of the lesion in the tonsil and pharyngeal mucosa. It seems most probable that they failed to recognize it.

Warthin was apparently unaware of the fact that the findings in the tonsils in the course of measles to which he attributed such great importance were observed and reported twenty years before his publication by Alagna,[4] who, in 1908, studied eight children, from 1 to 4 years old, who had died of measles, and reported his findings in 1911. He limited his study to the changes in the nose and throat, the other organs being studied by Ciaccio,[5] whose findings will be mentioned later. Alagna observed in the tonsils a change not seen in the normal organs. Without any definite topographic relationship, masses of nuclei were seen, consisting of groups of from eight to fifteen lying together, each with a distinct nuclear membrane. They resembled megakaryocytes. The picture described by Alagna is undoubtedly of the same nature as that observed and described by Warthin.

From the Pathological Laboratories and the Department of Surgery, Mount Sinai Hospital.

1. Warthin, A. S.: Arch. Path. **11**:864, 1931.
2. Ewing, James: J. Infect. Dis. **6**:1, 1909.
3. Mallory, F. B., and Medlar, E. M.: J. M. Research **41**:327, 1920.
4. Alagna, G.: Arch. f. Laryng. u. Rhin. **25**:527, 1911.
5. Ciaccio, Carmelo: Virchows Arch. f. path. Anat. **199**:378, 1910.

In the histologic studies on cases of measles published after 1911 there is no reference to the finding of giant cells in the tonsils until Warthin's publication. The report of Ciaccio [5] in 1910 was based on a study of the same eight cases of measles the rhinolaryngologic aspects of which formed the basis of Alagna's report. In Ciaccio's report, no mention is made of an examination of the intestines and particularly of the appendix. There is a casual note on the rare occurrence of cells resembling megakaryocytes in the lumina of new-formed capillaries in the interstitial tissue of the lungs. Secher,[6] in 1916, reported the autopsy findings in two persons who had died of enteritis during the course of measles. In his review, he quoted the report of Alagna, but did not state whether he had examined the tonsils in his own cases, nor did he mention an examination of the appendix. In the intestinal tract, the lymphatic tissues were swollen, particularly Peyer's patches, which resembled those seen in typhoid fever, but they were not ulcerated. There is a detailed microscopic report of the changes in the lymphatic tissue of the intestinal tract, but giant cells were not noted. Abramow [7] observed giant cells in the skin of patients who had died during the course of measles. He did not mention details concerning the structure of the giant cells, but a picture shows that they do not in the least resemble the giant cells seen in the tonsils. In Abramow's cases, the giant cells were not seen before the fourth day after the appearance of the rash.

After Warthin's article was published, Finkeldey [8] reported, in 1931, the finding of the characteristic giant cells in the tonsils removed operatively from a child 7 years old in whom clinical measles appeared three days after the operation. He referred to the publication of Alagna in 1911, but emphasized the fact that in his case the changes in the tonsils were already present in the prodromal stage of the disease, while in the cases of Alagna the tonsils were examined after the patients had died as a result of the disease. The same difference holds true for the four cases of Warthin.

Herzberg [9] reported in January of this year the finding of similar giant cells in the lymph follicles of an appendix that was removed from a child 6 years old. Four days following operation, a typical measly rash developed. Herzberg's report seems to be the first in the literature with a mention of the finding of giant cells in the appendix in the prodromal stage of measles.

The observation of a similar case in the Mount Sinai Hospital prompted us to place it on record.

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6. Secher, K.: Berl. klin. Wchnschr. **53**:250, 1916.
7. Abramow, S.: Virchows Arch. f. path. Anat. **232**:1, 1921.
8. Finkeldey, W.: Virchows Arch. f. path. Anat. **281**:323, 1931.
9. Herzberg, Mortimer: J. A. M. A. **98**:139, 1932.

CASE 1.—A boy 6 years old was admitted to the Mount Sinai Hospital in the service of Dr. H. M. Richter on May 17, 1929. His temperature on admission was 100 F.; his pulse rate, 112; his respiration rate, 24. There was pain in the right lower quadrant of the abdomen, accompanied with nausea and vomiting. The mother stated that the condition started on the evening before admission, with generalized abdominal pain, which then localized in the right lower iliac region and was associated with vomiting. Two days before that there was marked swelling of the cervical glands on the left side, which subsided on the following day. On physical examination there were slight congestion of the pharyngeal mucosa and tenderness in the right iliac region. The white blood cell count was 17,800, with 77 per cent polymorphonuclear leukocytes. The diagnosis of acute appendicitis was made, and the patient was operated on within one hour after admission. Dr. Richter, who performed the operation, described the appendix as being "large, thick, bulbous at distal end, soft, fluctuating and filled with pus." The diagnosis of the pathologist was "gangrenous appendicitis."

On the day following operation, the temperature began to rise, reaching 105.2 F. in the evening; the pulse rate was 138 and the respiration rate 40. Congestion of the mucous membranes of the mouth and swelling of the left cervical glands were noted. A moderate cough developed, with râles in the bases of the lungs. On the morning of the third postoperative day a rash appeared. The diagnosis of measles was made. The further course of the measles and the postoperative recovery were uneventful, and the child left the hospital on the ninth day following admission.

Reexamination of the histologic sections, prompted by the report of Herzberg, revealed changes as follows: The lymph follicles showed the central cell exhaustion mentioned by the previous authors. Numerous giant cells were present having the same appearance as those seen in the photographs published by Warthin, Finkeldey and Herzberg. They varied in size, in the number of the nuclei and in the distinctness of the surrounding protoplasm.

Herzberg emphasized in his report that he did not see migration of the giant cells into the mucosa. In our case, giant cells were present in the mucosa in considerable numbers, particularly in the subepithelial layer (fig. 1 *C*). Some were seen passing through the epithelial lining. The lumen was filled with an exudate consisting of neutrophilic leukocytes and fibrin. In the midst of it there was a clump of nuclei strongly suggesting a giant cell similar to the smaller variety seen in the mucosa. The mucosa and all the other layers were densely infiltrated by neutrophilic leukocytes. The finding of acute suppurative appendicitis coincident with the changes characteristic of measles is of considerable practical interest, emphasizing that appendiceal symptoms during the course of measles may be due to actual inflammation of the organ, requiring surgical interference, and that they should not be discounted lightly as being a part of the general clinical picture of measles.

Since this case was presented at the meeting of the Chicago Pathological Society, we have had the opportunity to study three additional cases. In the second case, the appendix was removed two days after the appearance of the cutaneous eruption of measles and at least four days after the onset of photophobia. The third was a case of appendicitis occurring during the prodromal stage of measles. In the fourth case, the appendicitis appeared, and the operation was performed, following recovery from measles.

CASE 2.—A boy 8½ years old was admitted to the Contagious Disease Department of the Cook County Hospital, in the service of Dr. B. M. Gasul, on April 27, 1932. He had been well till three days before admission; then a cough developed, followed by photophobia, and for the twenty-four hours preceding his admission to the hospital he experienced severe generalized abdominal pain, which became local-

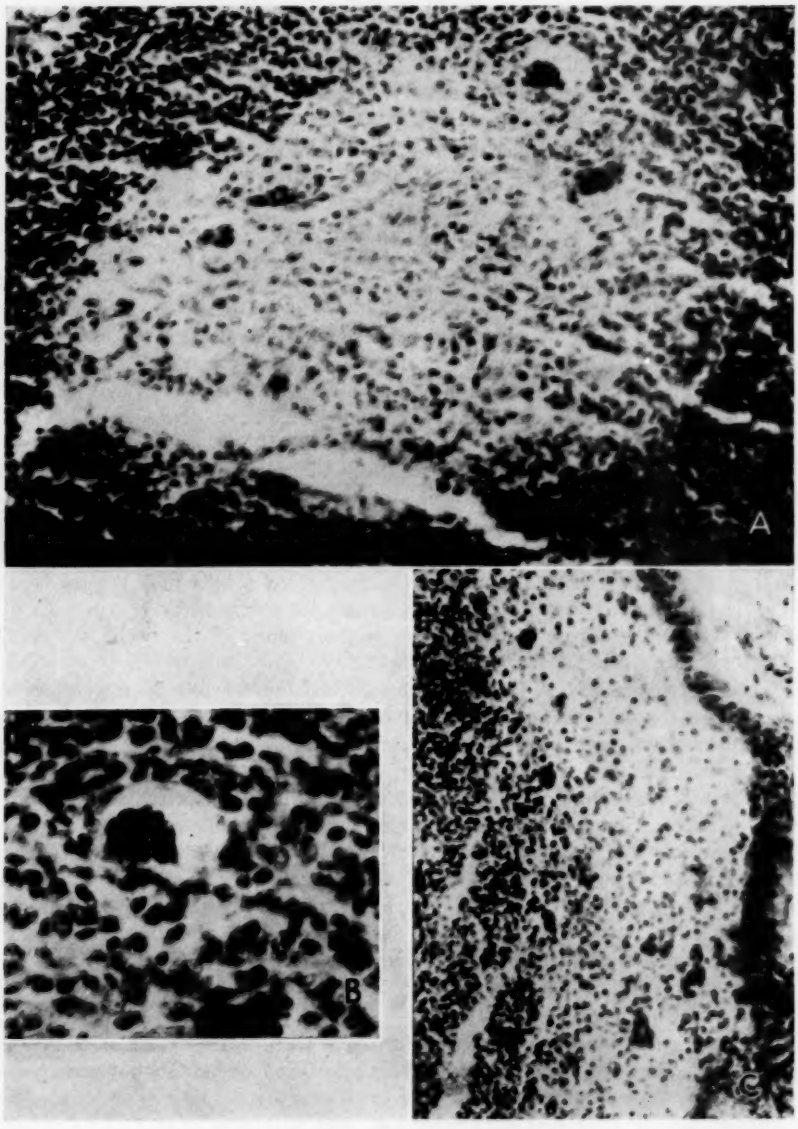

Fig. 1 (case 1).—*A*, photomicrograph showing a germinal center with three distinct giant cells; × 220. *B*, photomicrograph of a high power magnification of a portion of the area shown in *A*. It includes the giant cell seen at the upper border of the germinal center. The clumped nuclei of the giant cell are surrounded by a wide zone of clear protoplasm. *C*, photomicrograph showing the giant cells in the subepithelial layers of the mucosa. They are mainly of the smaller compact variety; × 120.

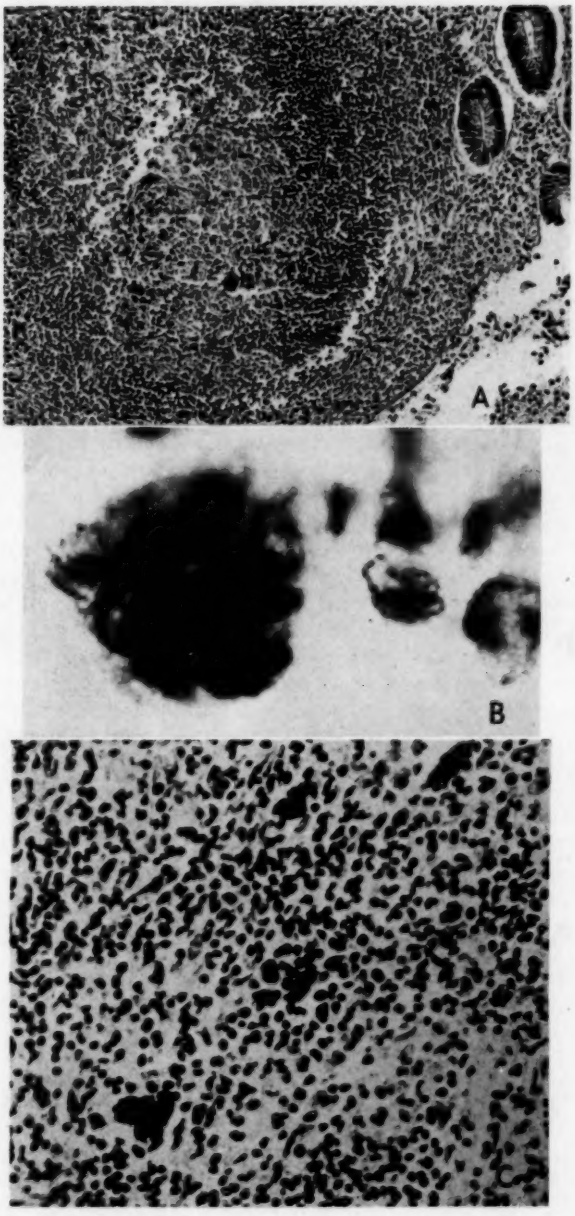

Fig. 2 (case 2).—*A*, photomicrograph showing a portion of the mucosa and a lymph follicle. The mucosa is diffusely infiltrated by neutrophilic leukocytes. A giant cell of the small compact variety is seen in the lower half of the follicle. The nuclei cannot be distinguished at this magnification; × 100. *B*, a higher magnification of the giant cell seen in *A*. Here five distinct nuclei can be seen. The protoplasm in this small compact variety is very scanty; × 1,800. *C*, photomicrograph showing a characteristic multinucleated giant cell in the left lower corner. The two other giant cells in the central portion and in the right upper corner are less distinct; × 320.

ized in the right iliac region on the morning of admission. At about the same time with the onset of the abdominal pain there appeared a generalized cutaneous eruption. When examined on admission, he had Koplik's spots; his rash was macular and papular, covering the trunk and face. There were localized marked tenderness in the right iliac region and slight rigidity. Examination of the blood showed: hemoglobin, 80 per cent; red blood cells, 4,300,000; white blood cells, 12,000. The urine was normal. The diagnosis of acute appendicitis and measles was made. At the operation, which was performed two days after the appearance of the cutaneous eruption, more than four days after the onset of photophobia, and over five days after the respiratory symptoms had set in, a gangrenous retrocecal appendix was found. The child made an uneventful recovery.

Slides prepared from one block showed diffuse infiltration by neutrophilic leukocytes and fibrin. A diagnosis of diffuse suppurative appendicitis was made by Dr. Perry G. Melnik of the Pathological Laboratories of the Cook County Hospital. Dr. Richard H. Jaffé, pathologist of the Cook County Hospital, kindly permitted us to study the remaining portion of the appendix. Serial sections were prepared. Most sections showed a very intensive, diffuse infiltration of all the layers of the wall by neutrophilic leukocytes and by fibrin, and extensive areas of necrosis leading to destruction of the mucosa and to marked desquamation of the epithelial and subepithelial layers. The normal histologic structure was obscured by the inflammatory infiltration. In a fair number of the sections, small multinucleated cells were found in the lymph follicles and in the subepithelial layers, resembling the small, compact, multinucleated cells seen in our first case. They had only a small number of nuclei (about from 3 to 6) and a scanty amount of protoplasm. With the help of high magnification, the single nuclei could be distinguished (fig. 2 *B*). In a small portion of one block, large, typical multinucleated giant cells were found in a lymph follicle (fig. 2 *C*).

The very small number of the characteristic giant cells found in this appendix, despite a study of serial sections of almost the entire specimen, is of considerable interest. It confirms the observation of Herzberg,[9] who was able to find giant cells in his case also only in a very limited portion of the appendix. The possible explanations of the scarcity of the giant cells will be discussed later.

Case 3.—A boy, aged 6, was admitted to the surgical department of the Michael Reese Hospital on May 28, 1932. His temperature had been elevated for the preceding two days, and for twenty-four hours he had been complaining of a sharp, continuous pain in the right iliac region. His previous history was irrelevant. When he was examined on admission, his temperature was 102.6 F.; his pulse rate, 140; his respiration rate, 40. The tonsils were enlarged and congested. No other changes were noted in the mucous membrane of the mouth. The cervical lymph glands were slightly swollen. There were tenderness and rigidity in the right iliac region. Examination of the blood showed: red blood cells, 4,400,000; white blood cells, 12,150; polymorphonuclear leukocytes, 82 per cent; lymphocytes, 18 per cent. In the urine, some acetone was found, but no other abnormalities. The diagnosis of acute appendicitis was made, and the child was operated on immediately. At the operation, an acutely inflamed appendix was found.

Dr. Otto Saphir, pathologist at the Michael Reese Hospital, examined the specimen. He found gross and microscopic evidences of acute diffuse suppurative appendicitis. Besides the inflammatory changes, there were numerous giant cells containing from 3 or 4 to 30 or more nuclei. The nuclei were closely packed with a narrow rim of free peripheral cytoplasm. The nuclear chromatin was abundant and

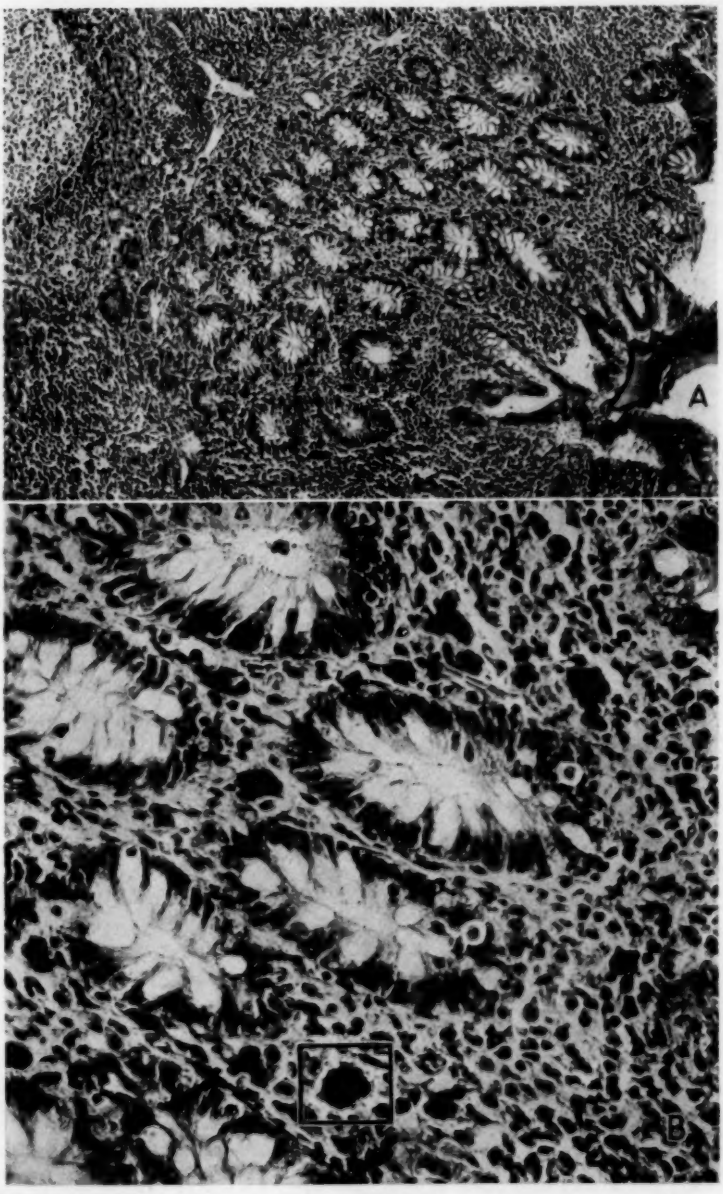

Fig. 3 (case 3).—*A*, low power photomicrograph showing large numbers of giant cells in the mucosa of the appendix; × 80. *B*, a high power magnification of an area reproduced in *A*; × 320.

coarsely trabeculated, strongly suggesting lymphocytic or plasma cell nuclei. The pathologic diagnosis was: "Acute diffuse suppurative appendicitis with giant cells in the appendix, characteristic of measles." Dr. Saphir's diagnosis was confirmed in the further course of the disease. Two days following the operation, a maculopapular rash appeared, and Koplik's spots were noted. There were 8,600 white blood cells. The diagnosis of measles was made. The child was isolated. The further course and recovery were uneventful. The child left the hospital on June 2, 1932.

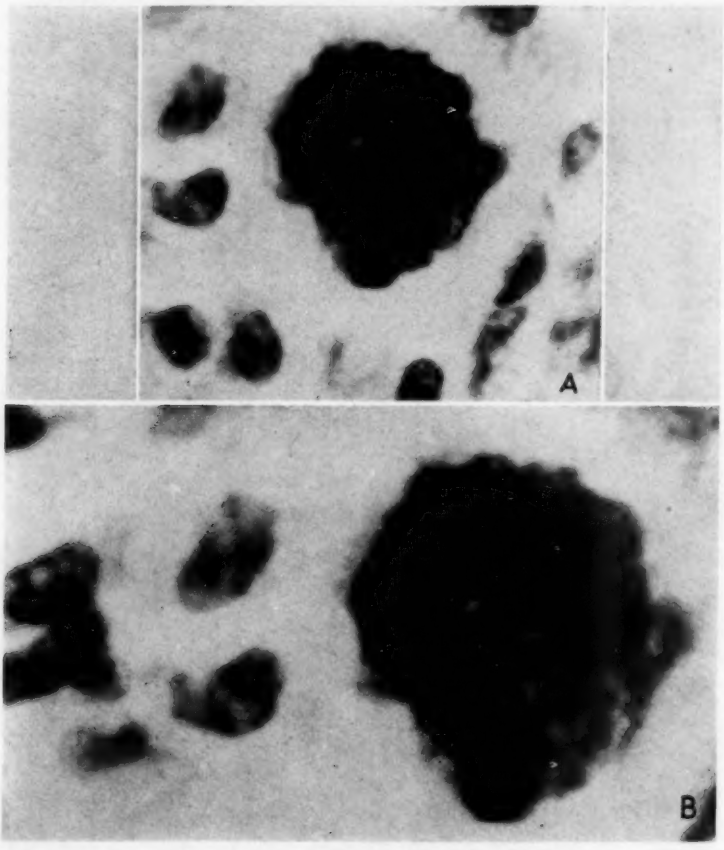

Fig. 4 (case 3).—*A*, a very high magnification of the giant cell seen in the lowermost portion of figure 3 *B*. The nuclei show a peripheral arrangement. The protoplasm is granular; × 1,600. *B*, the same as *A*; × 2,400.

Of the three blocks that were studied, two were the site of very intensive inflammatory changes, as described by Dr. Saphir, and in a large number of sections no giant cells could be detected. The third block, with only mild inflammatory changes, showed large numbers of the characteristic giant cells. In some sections up to 30 giant cells were counted in a low power field (fig. 3), but most fields had a lesser number. Only very few giant cells were seen in the lymph follicles; most of them were present in the mucosa, particularly in the subepithelial layers.

CASE 4.—A boy, 7 years old, was admitted to the Mount Sinai Hospital in the service of Dr. Philip L. Aries on May 19, 1932. About ten days previously Koplik's spots had appeared, and nine days previously a generalized cutaneous eruption had developed, diagnosed as measles. A younger child in the same family was recovering from measles. The disease in the case of the boy was mild. He had been out of bed for about four days when, on the evening before admission, he was seized with generalized abdominal pain, which soon became localized in the right iliac region. At the time of admission, there was marked tenderness with rigidity in the painful area. The temperature was 101 F. Examination of the blood showed 9,600 white blood cells, with 76 per cent polymorphonuclear leukocytes and 24 per cent lymphocytes. A diagnosis of acute appendicitis was made, and at operation an acutely inflamed, gangrenous retrocecal appendix was found. The further course and recovery were uneventful.

Histologic examination of the removed, grossly diseased appendix showed acute diffuse suppurative appendicitis and periappendicitis. Serial sections of the entire appendix were studied, but giant cells could not be found.

COMMENT

The abundance of the characteristic giant cells in the first and third cases of the series, their scarcity in the second and their complete absence in the fourth case suggest a relation between the presence of the giant cells in the lymph follicles and the subepithelial layers of the mucosa of the appendix and the stage of measles. In the two cases with the large numbers of giant cells the appendixes were removed two days before the appearance of the rash; in the second case, in which the giant cells were very scarce, the appendix was removed two days after the appearance of the rash, and in the fourth case, in which no giant cells were found, the appendix was removed nine days following the appearance of the cutaneous eruption. In the third case, the giant cells were found only in the parts of the appendix not markedly changed by the inflammatory process. While in the second case the relatively advanced stage of measles at which the appendix was removed was probably the main cause for the scarcity of the giant cells, the diffuse suppurative inflammatory process in the entire organ, which obscured the histologic relations and the cytologic details, may have been an additional factor.

SUMMARY

A histologic study was made of four appendixes, two of which were removed during the prodromal stage of measles, one during the course of the disease proper, and one after recovery. The presence of the characteristic giant cells in the mucosa and in the lymph follicles seems to have depended on the stage of the disease during which the organ was removed. The impression was gained that giant cells are rarely found in the portions of the appendix where profound diffuse inflammatory changes in the mucosa are present.

PRIMARY IDIOPATHIC MUSCULAR HYPERTROPHY OF THE ESOPHAGUS WITH NARROWING OF THE LUMEN

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Seven cases of primary idiopathic muscular hypertrophy of the esophagus with stenosis in which autopsy was performed have been recorded in medical literature. This condition is such a rarity, and the etiologic factors are so obscure that every new case reported may assist in elucidating its occurrence. I shall discuss briefly a case observed in the Stanford Medical Service at the San Francisco Hospital.

REPORT OF CASE

Clinical History.—P. N., an American grocer, aged 69, was admitted to the San Francisco Hospital on Aug. 16, 1929, complaining of pain that had been present in both legs for seven months, weakness and inability to walk. During the past four years his habits had been irregular, he had consumed large quantities of alcoholic liquors, his appetite had gradually "dropped off," he had had "gas on the stomach," and his food "had not digested." He had had occasional gagging when he tried to eat, but no vomiting. For three weeks he had had diarrhea. One week before his entry into the hospital he had gone to bed and had not been able to get out since. Prior to this he had never been sick.

He appeared undernourished. The lungs were clear. The heart was normal. The peripheral blood vessels were markedly sclerosed. The blood pressure was 115 systolic and 85 diastolic. Marked wasting of the extremities and hyperesthesia of the legs were present. The reflexes were normal. Urinalysis revealed a light cloud of albumin and occasional granular casts. The blood was normal, except for a white blood cell count of 67,000, with 64 per cent polymorphonuclear leukocytes and 32 per cent lymphocytes. The Wassermann reaction was negative.

The patient became progressively weaker. Five days after his entry, administration of a barium meal was attempted, but roentgen examination was unsatisfactory because the meal gagged the patient. Examination at a later date was suggested in order to rule out possible carcinoma of the esophagus. Following the meal, the man declined rapidly and died two days later.

The clinical diagnosis was: chronic alcoholism, malnourishment and dehydration, generalized arteriosclerosis and possible esophageal cancer.

Necropsy.—Necropsy was performed on the day of death. The body was that of a strongly built, emaciated man, aged 70, of medium stature.

The anterior mediastinal tissue, the parietal pericardium, and the epicardium over the right side of the heart contained a large amount of fat. The heart was about

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three-fourths normal size. The aorta showed marked atheromatosis. The lungs showed old apical scars and moderate anthracosis.

The mucosa of the trachea was smooth and regular, showing no fistulas or other abnormalities. The trachea measured 7 cm. from the cricoid cartilage to the bifurcation and was 5 cm. in circumference.

The esophagus was in normal position. On cut section there was marked hypertrophy of the muscular wall in the lower third, involving chiefly the inner or circular layer and producing marked narrowing of the lumen in this region (fig. 1).

Fig. 1.—A cut section of esophagus, showing the marked hypertrophy of the muscular wall in the lower third.

The esophagus measured 19 cm. from the level of the cricoid cartilage to the cardiac orifice into the stomach. Ten centimeters below the cricoid cartilage the wall of the esophagus measured 3 mm. in thickness, and from this level distally there was a gradual, symmetrical and uniform increase in thickness until at the cardia the wall measured 12 mm. in width. Of this, the inner muscle layer measured 7 mm., and the outer, 3 mm. The mucous membrane was smooth and intact throughout, and showed no diverticula, fistulas or areas of dilatation.

A crater-like shallow diverticulum, 1 cm. in diameter, was found in the cecum. The mucosa of the colon throughout showed a number of small ulcers, which ranged in size up to 6 mm. in diameter.

The stomach contained a small amount of yellowish mucus. A small amount of residual barium was found in the fundus.

The liver was small, measuring 20 by 16 by 6.5 cm., and showed a moderate amount of fat on section.

The anatomic diagnosis was: arteriosclerosis, general, moderate; hypertrophy of the esophagus, with narrowing of the lumen; colitis, acute, ulcerative; alcoholism, chronic; diverticulum of the cecum; tuberculosis, pulmonary, apical, healed; fatty liver.

Histologic Examination.—The esophagus (1 to 2 cm. above the cardia) showed marked hypertrophy of the longitudinal and circular muscle layers, especially of the

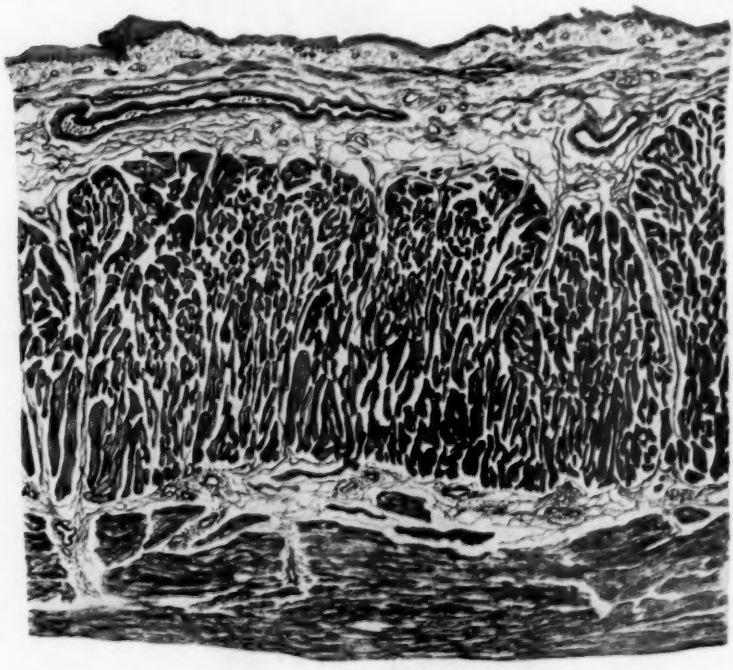

Fig. 2.—A microscopic section of the esophageal wall just above the cardia; × 8.

latter. The mucosal epithelium was of stratified, squamous type and of normal thickness. Some of the superficial cells showed beginning keratinization.

A longitudinal section of the hypertrophied area of the esophagus showed that the circular layer was about three times the width of the longitudinal (fig. 2). No round cell infiltration or other abnormalities were noted. The epithelium was of normal thickness and appearance. The papillae showed no abnormalities. The nerve ganglions were normal. The surrounding blood vessels showed a slight thickening of their walls.

The cardia was normal.

The liver showed moderate congestion with beginning atrophy of the central cells and moderate fatty infiltration.

SPECIAL FEATURES OF THE CASE

1. The age of the patient was 69 years; the sex, male.

2. There was no history of difficulty in swallowing, except for progressive failure of appetite during the past four years.

3. The heart was atrophied, and there were no enlarged mediastinal nodes or tumor masses that might have exerted pressure on the esophagus.

4. The esophagus was of normal length. Absence of diverticula, fistulas, etc., was demonstrated.

5. The hypertrophy was most marked in the circular muscle layer of the esophagus, beginning below the bifurcation of the trachea and becoming progressively greater, extending to the cardia.

6. The lumen of the area in which hypertrophy was present was narrowed.

7. There was no dilatation above the area in which hypertrophy and narrowing of the lumen occurred.

8. The cardiac orifice was normal, with no evidence of stricture or of obstruction.

9. There were no microscopic lesions in muscle, nerve ganglions, interstitial tissue and mucous membrane.

PATHOLOGY OF IDIOPATHIC MUSCULAR HYPERTROPHY OF THE ESOPHAGUS

In a review of the cases which have been reported in the literature and in conjunction with the case that I have described, I shall attempt to summarize briefly present knowledge concerning the occurrence and the nature of this type of esophageal hypertrophy. This condition may truly be rated among the pathologic curiosities. Owing to the vagueness or the absence of symptoms, it is difficult to make a diagnosis during life. For that reason all the known cases have been discovered at autopsy. In the seven cases previously reported the ages of the patients ranged from 39 to 68 years. Six of the patients were men; one, a woman.

Historically, this condition is discussed by the earlier authors, most of whom, however, had not seen actual cases.

Zenker and Ziemssen [1] up to 1878 had never observed a case of pure idiopathic muscular hypertrophy, although they conceded that such an independently occurring hypertrophy with stenosis was possible.

Förster [2] and Niemeyer [3] in 1865 stated that esophageal stenosis with muscular hypertrophy might occur, but that they believed it to be caused by "chronic catarrh."

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1. Zenker, F. A., and Ziemssen, H.: Handbuch der speziellen Pathologie und Therapie, Leipzig, F. C. W. Vogel, 1878.

2. Förster, A. J. T.: Handbuch der pathologischen Anatomie, Leipzig, L. Voss, 1863.

3. Niemeyer, F.: Lehrbuch der speziellen Pathologie und Therapie, Berlin, A. Hirschwald, 1865.

Birch-Hirschfeld [4] in 1887 wrote that in some cases of marked hypertrophy no reason for the stenosis was demonstrable.

Kitt [5] in 1895 mentioned the interesting occurrence of this condition in horses, namely, hypertrophy of the esophageal wall of as much as an inch in cross-section, converting the esophagus into a hard, thick, rigid tube. Interestingly, the condition involved chiefly the circular musculature.

Thus, in the older literature a few references to this condition can be found. However, these reports lack exhaustive descriptions, as well as accounts of microscopic examinations.

Recently, Henke and Lubarsch [6] included only two cases as well authenticated; these are the cases of Elliesen [7] and Ehlers.[8] For the period 1888 to 1930 I found described in the literature seven cases which I consider genuine and which were not associated with malignant change or with proximal dilatation. These are the cases of Pitt,[9] Rolleston,[10] Elliesen,[7] Ehlers,[8] Brücke,[11] Rake [12] and Goedel.[13]

ETIOLOGY OF HYPERTROPHY OF ESOPHAGEAL MUSCULATURE WITH NARROWING OF THE LUMEN BUT WITHOUT PROXIMAL DILATATION

Many etiologic and contributing factors in esophageal hypertrophy have been cited, such as: (*a*) simple overwork, due to the swallowing of large bites of food; (*b*) foci of nerve irritation, causing achalasia; (*c*) stenosis due to compression, i. e., by a hypertrophied heart, enlarged mediastinal nodes, an aortic aneurysm, etc.; (*d*) obstruction from within, obliteration stenosis, stenosis caused by carcinoma, annular hypertrophy; (*e*) stricture following erosion and chronic ulceration, and (*f*) chronic catarrh.

None of these many factors is common in the cases reviewed. Simple overwork and foci of irritation seem unimportant.

Compression stenosis can likewise be discarded, although its importance has been emphasized by several authors. Pitt [9] and Wilks and

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4. Birch-Hirschfeld, F. V.: Lehrbuch der pathologischen Anatomie, Leipzig, F. C. W. Vogel, 1887.

5. Kitt, Theodor: Lehrbuch der pathologischen Anatomie, Stuttgart, F. Enke, 1895.

6. Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4, p. 105.

7. Elliesen: Virchows Arch. f. path. Anat. **172**:501, 1903.

8. Ehlers: Virchows Arch. f. path. Anat. **184**:512, 1907.

9. Pitt, G. N.: Tr. Path. Soc. London **39**:109, 1888.

10. Rolleston, D. D.: Tr. Path. Soc. London **50**:69, 1899.

11. Brücke, E. T.: Virchows Arch. f. path. Anat. **270**:880, 1928.

12. Rake, G. W.: Guy's Hosp. Rep. **166**:145, 1926.

13. Goedel, A.: Wien. med. Wchnschr. **79**:967, 1929.

Moxon [14] noted association of hypertrophy of the esophagus with that of the heart. Against compression by mediastinal masses are their absence in this series of cases and their common occurrence as compared with the incidence of the esophageal lesion.

Obstruction from within does not occur in this series. Greigh [15] pointed out that in cases with obstruction from within, the outer as well as the circular muscle layer is hypertrophied. He attempted to distinguish between the hypertrophy occurring subsequent to congenital stenosis and that in the cases of so-called idiopathic dilatation. In the former, the hypertrophy affects both longitudinal and circular layers; in the latter, only the circular.

Brücke [11] advanced the theory that the condition is equivalent to diffuse myoma, but this was denied by Goedel,[13] who said that it is wrong to speak of "diffuse myoma of the esophagus," since the change is concerned with a quantitative increase only, which in every respect is of regular growth.

Chronic catarrh was for a long time held to be associated with muscular hypertrophy of the esophagus, but this idea has been generally abandoned.

Niemeyer [3] stated that stenosis of the esophagus may at times depend on hypertrophy of the musculature and interstitial connective tissue. The mucosa is always simultaneously thickened with the increase in connective tissue and nonuniformly swollen.

Roe [16] reported a case in which there was an increase in the thickness of the esophageal wall in the vicinity of the tracheal bifurcation. Microscopically, the muscular fibrillae had become degenerated and had been replaced by a connective tissue formation. Therefore, the actual condition was pseudohypertrophy.

Goedel [13] inclined to the hypothesis of an embryonic anomaly,—of a primary congenital disturbance of growth in the sense of an inclination of the esophageal musculature to overgrowth. He believed that the "endogenous factor of the individual, inborn predisposition to increased growth," plays an important rôle in the case of all hypertrophies, even the acquired.

Elliesen,[7] having reviewed all the possibilities, found no satisfactory explanation, and therefore felt justified in saying that the condition appeared to be idiopathic, affecting chiefly the male sex, and occurring in middle or later life.

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14. Wilks and Moxon: Tr. Path. Soc. London **39**:107, 1888.
15. Greigh, D. M.: Edinburgh M. J. **26**:342, 1921.
16. Roe, J. O.: New York M. J. **53**:289, 1891.

COMMENT

A clear distinction should be made between the cases discussed here and those with dilatation of the esophagus (esophagectasia), which are recognized not infrequently and are by no means uncommon. Although the two conditions are anatomically different and vastly apart in incidence, they have common developmental factors. One might even be inclined to propose the thesis that they are manifestations of the same process, dilatation occurring as a sequel to hypertrophy and stenosis. Symptoms as a rule do not arise until the dilatation has become well established.

Probably the most nearly correct interpretation is that the muscle hypertrophy occurs as the result of a completely compensated achalasia [17] of the esophagus. This hypothesis was first suggested by Dr. Brown Kelly and Prof. S. G. Shattock [18] in discussing Rolleston's case.[10] This would place the hypertrophy as one of the sequelae of "cardiospasm." [19]

In the majority of cases of both conditions, that is, hypertrophy with narrowing of the lumen and ectasia, no lesions are found, the cause of the obstruction, if existent, being attributed to functional disturbances. In only one of the cases in this series [12] were microscopic lesions found. Sir Arthur Keith, who examined Rake's slides, noted that the large size of the ganglions present was similar to that found in ganglions near the pelvic-rectal sphincter in Hirschsprung's disease, and Hurst [18] expressed the belief that the latter condition is due to an achalasia of the pelvic-rectal junction. Hurst also expressed the belief that the majority of cases of esophageal achalasia are due to progressive organic disease involving Auerbach's plexus in the lower part of the esophagus. In Rake's case, the most advanced lesions were in the plexus below the hypertrophy, possibly leading to lack of coordination or spasm of the esophagus in the diseased portion. As a result, hypertrophy occurred proximally.

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17. Achalasia, failure to relax, defined by Hurst (Proc. Roy. Soc. Med. **12**:34, 1918) as a functional stenosis due to failure of the cardia to relax.

18. Shattock, S. G.: Proc. Roy. Soc. Med. **12**:95, 1918-1919. Hurst, A. F.: Proc. Roy. Soc. Med. **12**:34, 1918.

19. Cardiospasm, increased muscular tonicity or spasm of the musculature at the cardia. There is much discussion in the literature as to which condition is primary, cardiospasm or phrenospasm. The latter is a functional spasm of the musculature of the crura forming the margins of the hiatus, resulting in stenosis at the diaphragm—the stenosis, therefore, not being primarily esophageal (Jackson, Chevalier: Proc. Roy. Soc. Med. **12**:35, 1918-1919. Hill, G. W.: ibid, p. 66). For the purpose of this paper, however, it suffices to say that general ectasia of the thoracic gullet is secondary to primary obstruction of one or the other portions of the phrenocardiac segment of the esophagus, brought about by muscular malaction or overaction.

Hypertrophy occurs as long as compensation is maintained, then dilatation. This is analogous to what happens with the heart in hypertension, and with the urinary bladder in obstruction, and, in fact, is true of any tubular-muscular organ. Nerve lesions are not necessary, because there may be an inherent failure of the muscle to maintain compensation.

Those cases in which the hypertrophy commences above the cardia may be explained satisfactorily on the basis of the compensated achalasia. However, in those cases in which the hypertrophy continues into the cardia this explanation hardly seems satisfactory.

CONCLUSION

Cases of ectasia occur in all age groups, whereas those of hypertrophy with stenosis have been observed so far only in persons past 39 years of age and chiefly in the male sex. If the two were related to each other, hypertrophy should be found in the earlier age group. As Goedel [13] has written, "there seems to be some inherent, congenital factor which determines the occurrence and tendency for hypertrophy in 'idiopathic' as well as in acquired hypertrophies." The wide variation in the degree of the hypertrophy that occurs under similar given conditions is well known. As to the ultimate reasons for these inherent variations and for the achalasias, one is still in the dark. It will suffice here to say, however, that these two factors, first, the congenital tendency to hypertrophy, and second, the development of a functional, completely compensated achalasia, may be of some importance in the muscular hypertrophy with narrowing of the lumen. In conclusion one has to acknowledge that no adequate explanation at present is available, although the hypothesis of a completely compensated achalasia may have some merit.

SUMMARY

A case of primary muscular hypertrophy of the esophagus affecting chiefly the circular layer, and accompanied by narrowing of the lumen, has been reported. The literature has been reviewed and searched for reports of similar cases, and several have been found. The views pertaining to the etiology of muscular hypertrophy with stenosis have been presented. The relation of this condition to ectasia of the esophagus has been discussed. The condition must still be considered as "idiopathic" until more is known of possible congenital tendencies to excessive development, and of the relation of the condition to achalasia of the esophagus.

INFLUENCE OF LIVER EXTRACT AND ACUTE INFECTION ON THE RETICULOCYTES AND BONE MARROW OF PIGEONS

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In their first series of patients with pernicious anemia who were treated by liver therapy, Minot and Murphy [1] noted that infection inhibited the prompt reticulocyte response and the general improvement ordinarily obtained. This observation has subsequently been confirmed by many other investigators.[2] The exact mechanism, however, of the action on the bone marrow and the blood of the substance effective in pernicious anemia, as well as of the neutralizing effect of infection on the reticulocyte response, is still obscure.

The experimental approach to the question of the mechanism of the action of the principle effective in pernicious anemia has yielded little positive information. The potent material does not significantly influence the peripheral blood of normal rats,[3] rabbits and dogs.[4] Neither in anemias experimentally produced in mammals has any significant effect been obtained which could be ascribed to the action of the principle effective in pernicious anemia.[5] However, pigeons seem to be peculiarly sensitive to the potent material, and it has been shown [6] that relatively pure liver extracts injected intravenously, as well as commercial liver extract no. 343 (N. N. R.) fed by mouth, cause a typical reticulocyte response in normal pigeons. It was also noted that one bird that failed to show an increase in reticulocytes had a severely ulcerated mouth. It

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The expenses of this investigation were defrayed in part by the J. K. Lilly gift to the Harvard Medical School.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. Minot, G. R., and Murphy, W. P.: J. A. M. A. **87**:470, 1926.

2. (*a*) Vaughan, J. M.: Quart. J. Med. **23**:90, 1930. (*b*) Davidson, L. S. P., and Gulland, G. L.: Pernicious Anaemia, London, Henry Kimpton, 1930.

3. Vaughan, J. M., and Muller, G. L.: J. Clin. Investigation **11**:129, 1932.

4. Adlersberg, D., and Gottsegen, G.: Arch. f. exper. Path. u. Pharmakol. **142**:323, 1929.

5. Vedder, A.: Nederl. tijdschr. v. geneesk. **72**:4411, 1928. Vedder A.: Ergebn. d. inn. Med. u. Kinderh. **38**:272, 1930. Orban, M.: Monatschr. f. Kinderh. **42**:402, 1929. Robscheit-Robbins, F. S.: Physiol. Rev. **9**:666, 1929. Davidson and Gulland.[2b]

6. Vaughan, J. M.; Muller, G. L., and Zetzel, L.: Brit. J. Exper. Path. **11**:456, 1930.

therefore seemed as if sepsis, interfering with the response to the principle effective in pernicious anemia in man, might also play the same rôle in pigeons.

To elucidate further the action of liver extract on the red blood cells in the bone marrow, and to obtain some possible explanation for the failure of an adequate reticulocyte response in patients with pernicious anemia who were suffering from infections, a series of experiments has been carried out with the pigeon as the experimental animal. This paper deals with influence of acute infection and of administration of liver extract on the reticulocytes in the peripheral blood and on the histologic changes occurring in the bone marrow of pigeons.

METHODS

Healthy adult pigeons were used throughout. They were kept under standard laboratory conditions in individual cages and supplied daily with fresh water and a food mixture obtained in the market under the name of "pigeon feed." Grit was also supplied. On this regimen, untreated adult birds maintain their weight and general appearance of well-being indefinitely. All the animals were allowed to become stabilized as to weight and composition of the blood before the experiment was begun. These precautions are necessary because it has been found in this laboratory that young birds, in some instances, maintain a high reticulocyte count up to 6 months of age, and pigeons received in poor condition from the market respond with a reticulocyte rise when put on an ample diet.

The total number of red blood cells were counted and the hemoglobin content was determined at frequent intervals, and a smear of blood was taken almost daily for a count of the reticulocytes. At various stages, tissues from the liver, spleen and bone marrow were obtained by autopsy. The character of the tissues fixed in Zenker's fluid and stained with eosin and methylene blue (methylthionine chloride, U. S. P.), was correlated with the state of the peripheral blood. The radial bone marrow was used for comparisons, because this marrow in most healthy adult birds is mainly fatty, and increased hyperplasia and extension of the marrow can therefore be determined with ease. In a small number of animals, intravital puncture of the bone marrow was performed under local anesthesia before the infection or the administration of liver extract, in an attempt to correlate the changes of the bone marrow before and after the experimental procedure in the same animal. So as not to introduce an extraneous factor, only birds with minimal bleeding at the biopsy were employed.

In all, ninety-six pigeons were used. They were divided into three groups, which were given: (1) Staphylococcus aureus infection intramuscularly, (2) liver extract no. 343 (N. N. R.) by mouth, and (3) both infection and liver extract.

1. EFFECT OF INFECTION ON THE RETICULOCYTES AND THE BONE MARROW

The organism used was obtained from a fatal case of Staph. aureus septicemia in man, and only this one strain was employed. Sixteen hour broth cultures were injected into the pectoral muscle in doses of from 0.5 to 1 cc. As a rule, 0.75 cc. was employed, as 0.5 cc. did not call forth striking changes, and 1 cc. doses were often fatal. In all,

thirty-four pigeons were used in this group, ten of which died in from twenty-four to forty-eight hours after the injection—a mortality of 29.4 per cent. In the case of a few animals dying from the infection and killed in the agonal stage, the organism was recovered from the heart's blood in pure culture. In sixteen birds the temperature was taken daily, and a definite reaction to the infection, manifested by fever, was observed. The white blood cells responded to the pyogenic infection with leukocytosis, a reaction similar to that found in most animals and in man. Here the attention, however, has been focused mainly on two features, namely, the action of the infection on the reticulocytes in the peripheral blood and the simultaneous reaction of the bone marrow.

The normal reticulocyte count of healthy *adult* pigeons under the standard conditions in this laboratory usually has been from 10 to 12 per cent. After infection had been introduced, there was a decrease in the percentage of reticulocytes in the peripheral blood. This decrease seemed to be commensurable with the severity of the infection, the lowest percentage of reticulocytes being obtained between the third and fifth days of the infection. At about the eighth to the tenth day of the infection, there was, however, an increase in the percentage of reticulocytes in the peripheral blood above normal values, the highest point being reached between the twelfth and seventeenth days with values ranging between 25 and 35 per cent. Then the percentage of reticulocytes decreased gradually until a normal level had been established. This reaction of the reticulocytes to infection is illustrated in the first part of the curve shown in figure 1. The reason for this outpouring of young reticulocytes in the peripheral blood became clear when bone marrows were examined at various stages after infection.

As has been pointed out, the normal radial bone marrow in the adult pigeon is mainly fatty with some cellularity at the edges. Occasionally the entire marrow is hyperplastic. This condition is usually associated in the healthy adult bird with a partial or total replacement with cancellous bone of the normally hyperplastic femoral bone marrow. To exclude this factor the femoral bone marrow was examined in every instance. Under ordinary conditions, however, increased activity and extension of the hematopoietic tissue can be easily discerned in the radial marrow. Throughout the comment, the nomenclature of Sabin [7] has been employed, and in evaluating any changes in the bone marrow both quantitative and qualitative aspects have been considered.

In the normal bone marrow of pigeons, the centers of red blood cell production consist of a mixture of cells ranging from megaloblasts to mature red blood cells. A considerable proportion of the cells are

7. Sabin, F. R.; Doan, C. A., and Cunningham, R. S.: Contrib. Embryol. **16**:125, 1925.

found to be in the megaloblastic and early erythroblastic stage, and considerable activity is present, as evidenced by mitotic figures. These centers of erythrocytic production in pigeons are definitely circumscribed, while the white blood cells present, mainly in the form of myelocytes or adult leukocytes, are scattered in between without any definite arrangement. Typical pictures of radial bone marrows from normal pigeons are illustrated in figure 2, *A* and *B*, showing various degrees of cellularity.

Twenty-four hours after a bird had been infected, the bone marrow had become actively *stimulated*. Between the fat cells appeared many

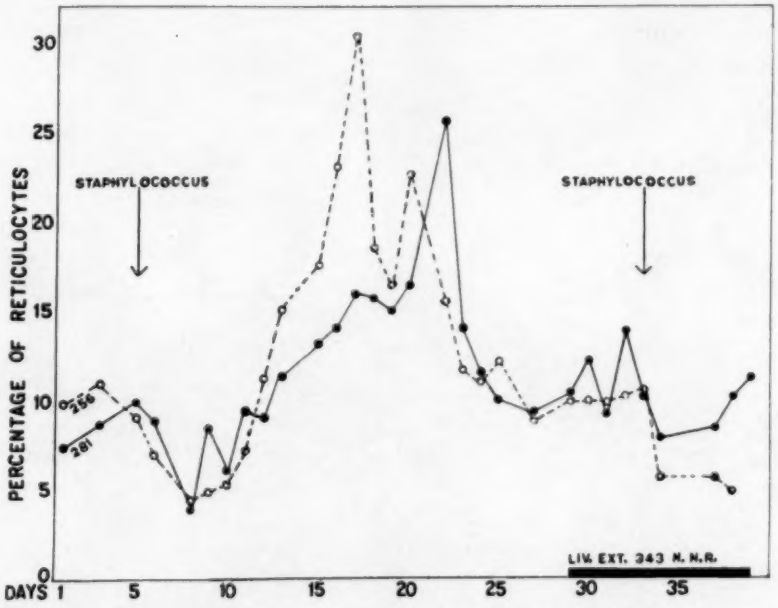

Fig. 1.—Reticulocytes of two pigeons (256 and 281) infected by injection of 1 cc. of a sixteen hour broth culture of Staph. aureus. Subsequently liver extract no. 343 (N. N. R.) was given by mouth, and the birds were reinfected.

immature cells belonging to both the red and the white blood cell series. The blood vessels were dilated. After forty-eight hours, the blood vessels remained engorged, and the hyperplasia was increased, with both the red and the white blood cells participating. The erythrocytic centers were distinguished in this early stimulated marrow by their situation in intersinusoidal capillaries, and by their more intense staining with methylene blue, as well as by nuclear and protoplasmic characteristics. The architecture of the bone marrows, twenty-four and forty-eight hours after infection, is illustrated in figure 2, *C* and *D*. With the oil immersion lens, mitotic figures were seen everywhere

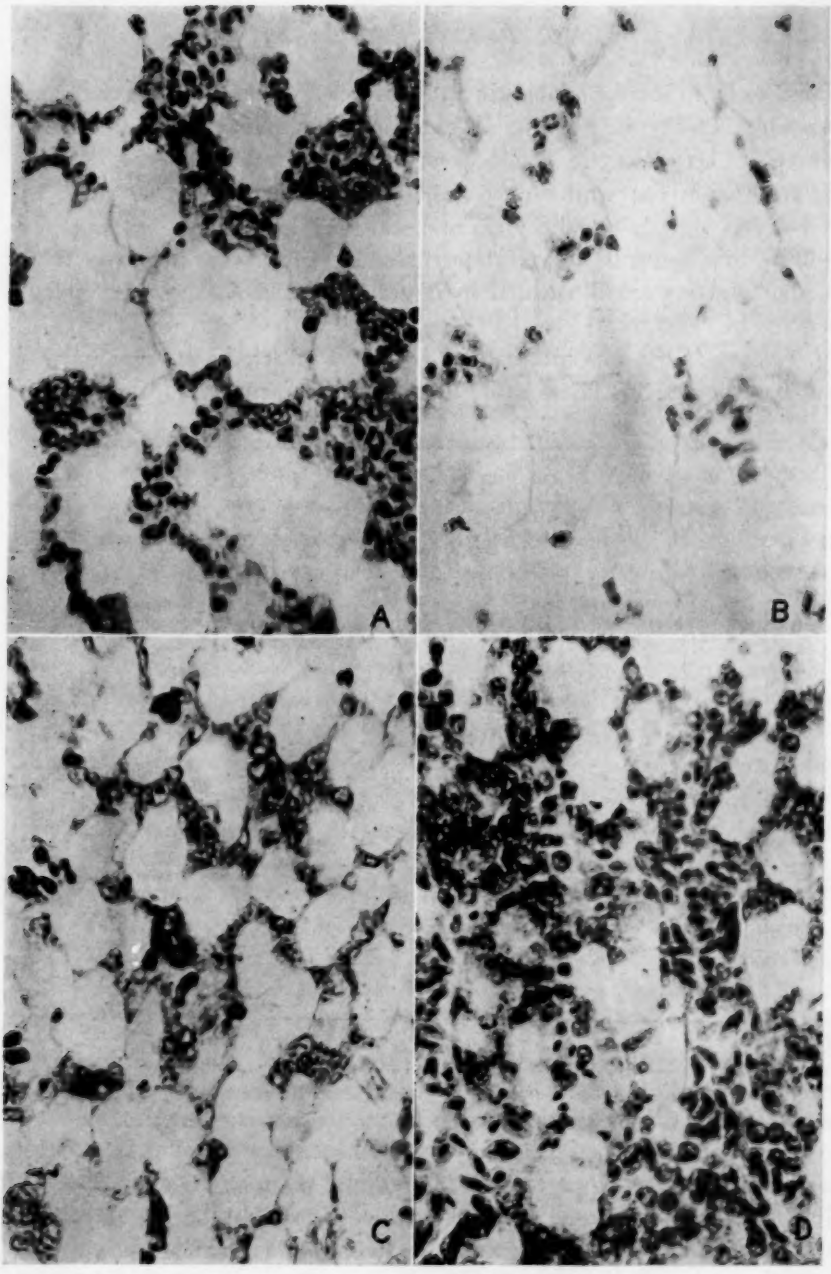

Fig. 2.—Appearance of marrow: *A*, moderately hyperplastic radial marrow of a normal pigeon with centers of production of red blood cells containing many megaloblasts; × 500. *B*, fatty radial marrow of a normal pigeon; × 500. *C*, marrow of a pigeon twenty-four hours after the pigeon had been infected by an intramuscular injection of Staph. aureus. It shows active stimulation of both white and red blood cells and hyperemia; × 500. *D*, marrow of a pigeon after the pigeon had been infected with Staph. aureus for forty-eight hours. Note the increased hyperplasia of both white and red blood cells and the dilated vessels; × 500.

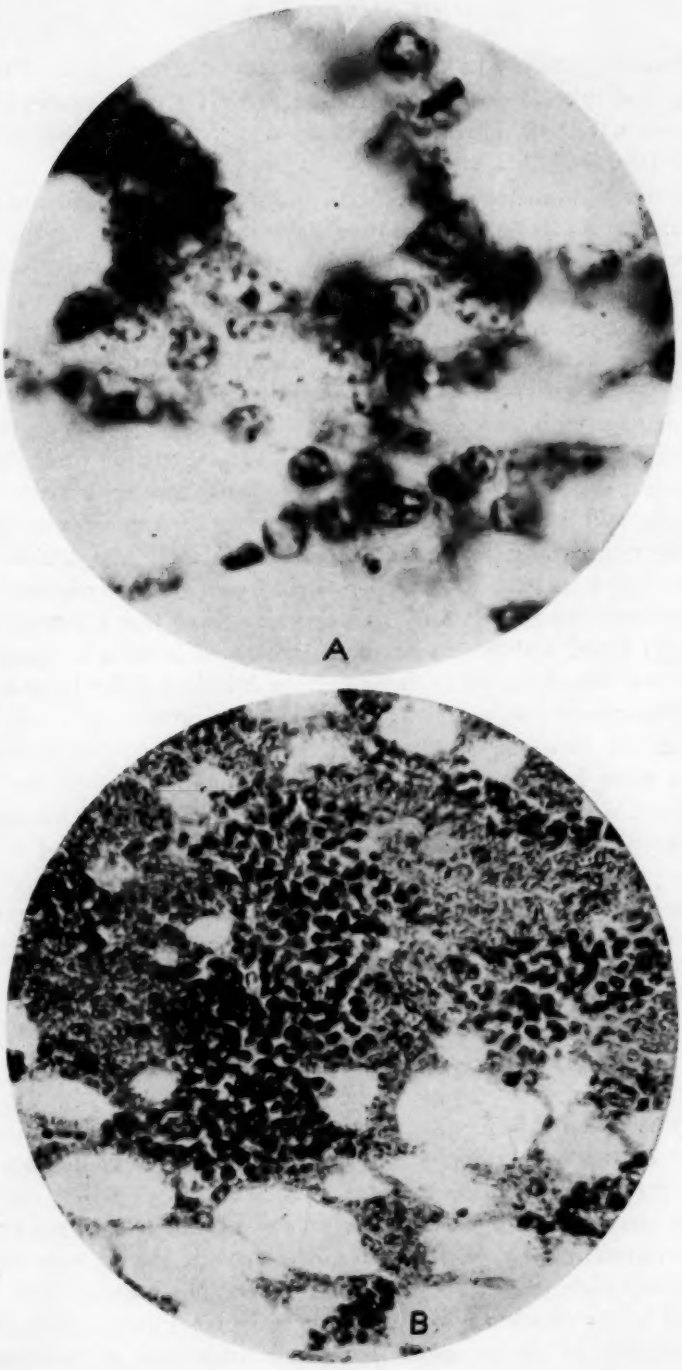

Fig. 3.—Appearance of marrow: *A*, specimen shown in figure 2 *D*; × 1,500. Note the megaloblasts with mitotic figures. *B*, radial marrow of a pigeon after the pigeon had been infected with Staph. aureus for five days. There is solid hyperplasia of both red and white blood cells; × 500.

among the erythrocytic as well as the myelocytic series. It is of interest to note that mitosis occurred at the edges of fat cells, where usually, in the normal bird, only the elongated nuclei of endothelial cells are present (fig. 3 *A*).

A progressive increase in cellularity was seen on the third and fourth days, and after an interval of five days the cellularity of the radial marrow had increased tremendously. The islands of red blood cells were large and consisted of quite immature cells around the periphery, while in the center some practically mature cells were present. The character of such a bone marrow is shown in figure 3 *B*. On the seventh day a hyperplasia was seen quantitatively identical with that on the fifth day, with, however, some qualitative changes. The reaction of white blood cells had subsided, while the centers of production of red blood cells were even larger and more prominent with many immature cells still present. The bone marrow apparently was rapidly becoming ready to discharge the excess of red blood cells, and evidence of this discharge was obtained by the outpouring of reticulocytes in the peripheral blood (fig. 1). Subsequently there was a return of the peripheral blood and bone marrow to a normal histologic appearance. No reaction was observed in the peripheral blood or in the bone marrow after intramuscular injection of 1 cc. of sterile broth.

From the foregoing observations one may be justified in concluding that acute infection causes an active stimulation of both the white and the red blood cell series of the pigeon's bone marrow. This response of the erythrocytes later takes expression in an outpouring of reticulocytes, apparently commensurable with the number of red blood cells that have been produced in the marrow. The phase of decreased percentage of reticulocytes in the peripheral blood corresponds to the rapid growth of the megaloblasts and early erythrocytes in the bone marrow.

2. EFFECT OF ADMINISTRATION OF LIVER EXTRACT NO. 343 (N. N. R.) ON THE RETICULOCYTES AND THE BONE MARROW

To this group of pigeons, thirty in all, 2 cc. of a 50 per cent solution of liver extract was administered daily by means of a stomach tube, after a preliminary control period.

Previous observations [6] on the response of the reticulocytes to the administration of substances effective in pernicious anemia were verified. In most instances, the count of reticulocytes at the peak of their initial response in the pigeons under the laboratory conditions employed was in the vicinity of 20 per cent. This same magnitude of response was obtained also with comparatively pure liver extracts.[6]

The bone marrow of a pigeon that had had liver extract for four days by mouth is illustrated in figure 4 *A*. At this time one would

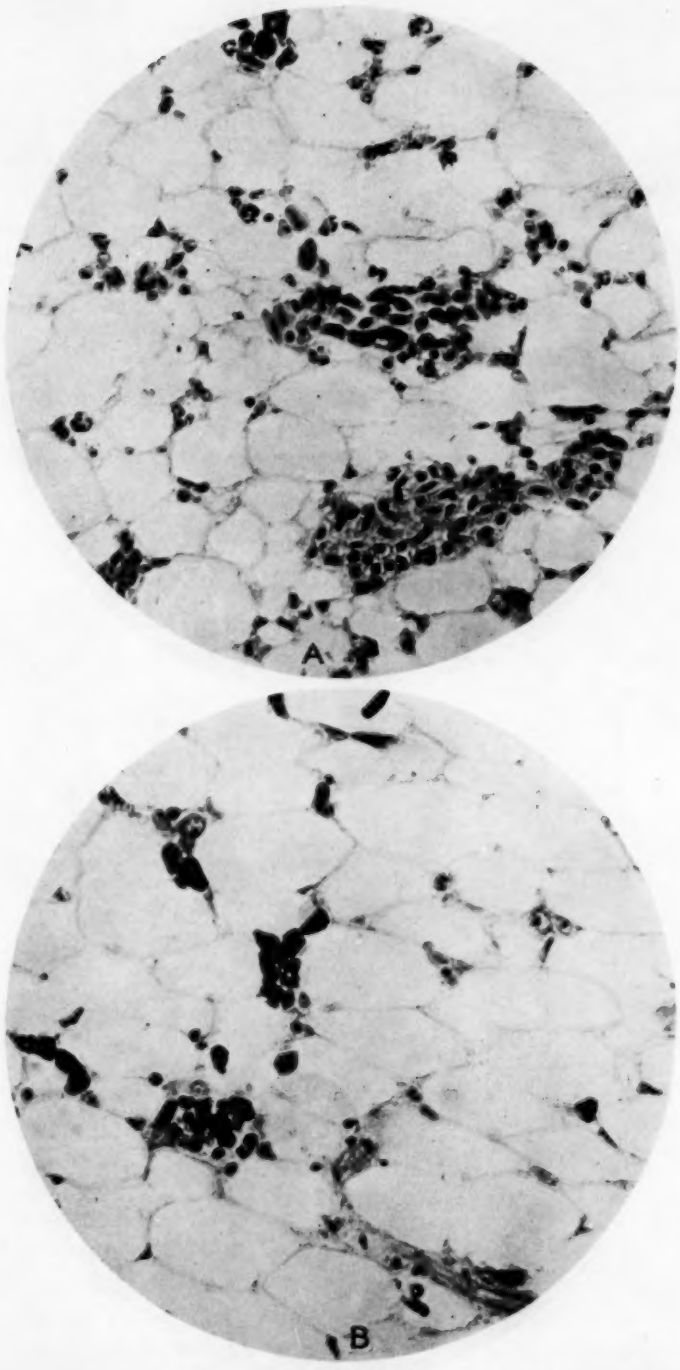

Fig. 4.—Appearance of marrow: *A*, radial marrow of a pigeon that had received liver extract daily for four days. Note the changed character of the two centers of production of red blood cells in the lower right sector. Practically all the cells are normoblasts; × 500. *B*, radial marrow of a pigeon that had received liver extract for seven days. Note the aplastic character of the radial marrow obtained when reticulocytes were 20 per cent in the peripheral blood; × 500.

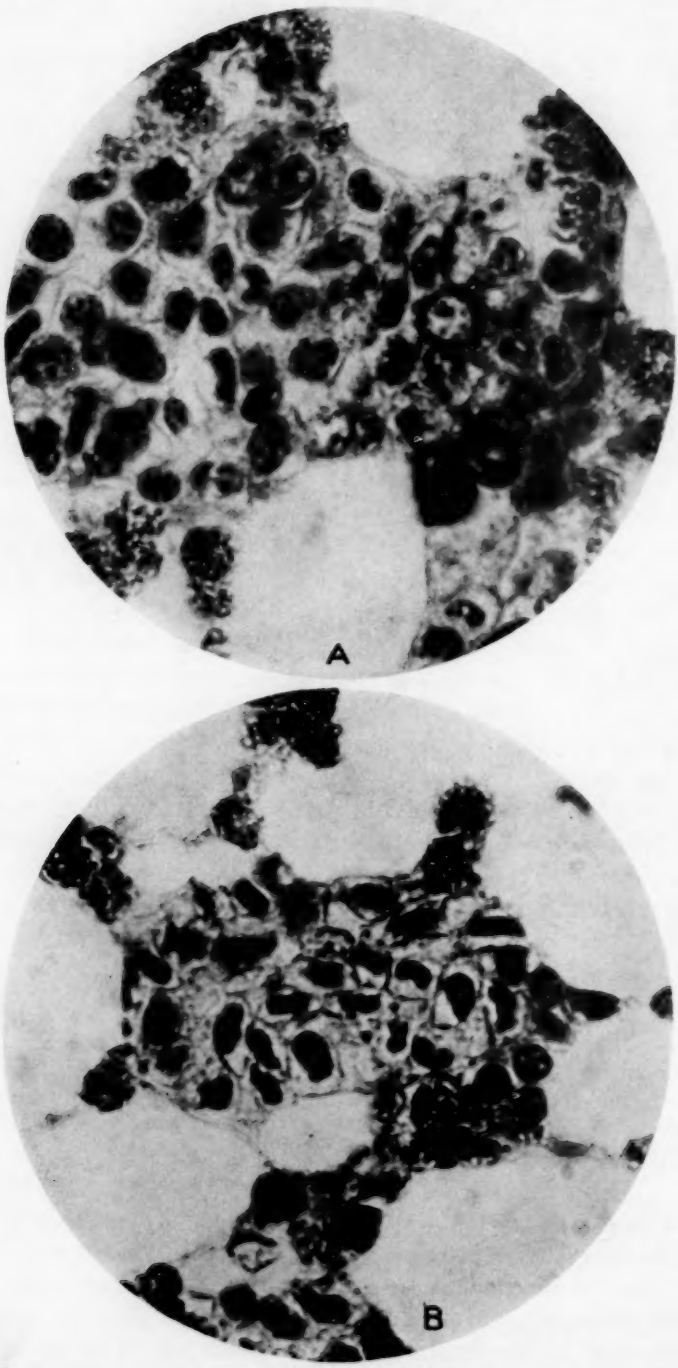

Fig. 5.—Appearance of marrow: *A*, normal center of production of erythrocytes showing megaloblasts, erythroblasts, normoblasts and mitotic figures; × 1,500. *B*, center of production of erythrocytes from a pigeon that had received liver extract by mouth daily for sixteen days. Note the absence of megaloblasts. A few erythroblasts are present, but the majority of the cells are in the normoblastic stage; × 1,500.

expect an increase and extension of the erythropoietic tissue to herald the reticulocyte increase in the peripheral blood. However, no stimulation was discernible from either the quantitative or the qualitative point of view. There seemed to be rather a diminution of megaloblasts, or immature red blood cells, and the centers of erythrocytic production consisted mainly of mature or nearly mature red blood cells.

Figure 4 *B* shows the radial bone marrow of a bird on the seventh day after the commencement of administration of liver extract. No

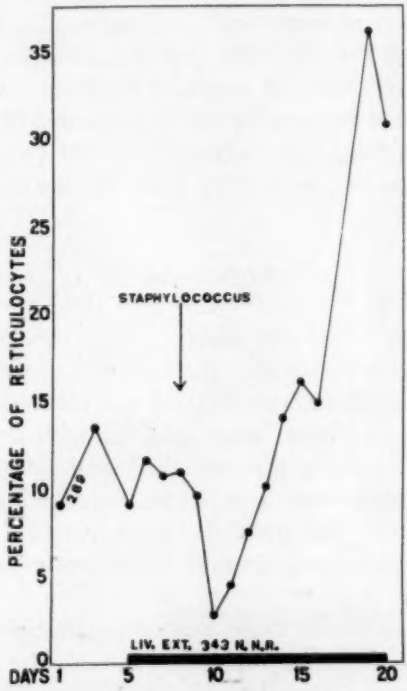

Fig. 6.—Reticulocyte response of a pigeon (289) given liver extract no. 343 (N. N. R.) and infected with an injection of a broth culture of Staph. aureus. Note the decrease of reticulocytes and the subsequent increase to 35 per cent.

comment beyond the descriptive legend is necessary. Identical results were obtained at intermediate periods up to sixteen days, the interval of time covered in these experiments. In no instance was there a stimulation of the erythroblastic tissue; rather a qualitative change in the islands of red blood cells was observed, with a diminution of megaloblasts and mitotic figures, as far as could be determined by counts on fixed and stained specimens. Quantitatively there appeared to be a decrease of erythropoietic tissue.

The contrast between the composition of a comparatively large center of production of red blood cells in the femoral bone marrow in a healthy bird without any treatment and that in a pigeon receiving liver extract by mouth daily for sixteen days is illustrated by figure 5 *A* and *B*. The absence or numerical diminution of megaloblasts in the bird receiving liver extract and the absence of evidences of activity, such as mitotic figures, were, to say the least, striking. Megaloblasts and mitotic figures are always present in the bone marrow of normal pigeons. Liver extract apparently transforms the pigeon's bone marrow from a megaloblastic to a late erythroblastic and normoblastic one, at least temporarily. This is accompanied by an outpouring of reticulocytes in the peripheral blood probably due to a simultaneous development of a large number of red cells of approximately the same age. At this stage, the reticulocyte response is not accompanied by increased activity in the sinusoidal endothelium to replace the lost cells; rather inactivity is present, as far as can be judged from the histologic picture of the bone marrow.

3. INFLUENCE OF LIVER EXTRACT NO. 343 (N. N. R.) AND INFECTION ON THE RETICULOCYTES AND THE BONE MARROW

In this group of thirty-two pigeons, 2 cc. of liver extract no. 343 (N. N. R.) was given daily for from three to seven days before the bird was infected, and its administration was continued until the animal was killed. Of these, three were infected with the organism intramuscularly on the same day that the administration of liver extract was begun. This procedure was discontinued, since the infection under these circumstances became altogether the predominating feature. Of the thirty-two birds infected, twelve died within forty-eight hours—a mortality of 37.5 per cent.

In birds infected before there was any appreciable rise in reticulocytes from the administration of liver extract, the reticulocyte curve obtained could not be distinguished from the one resulting from infection alone. There was the initial decrease of reticulocytes below the normal level and then there was an increase up to from 25 to 35 per cent. This is illustrated in figures 1 and 6.

When a reticulocyte response to the liver extract had been obtained, and the birds were infected at the presumable height of this response, the reticulocyte curve descended precipitously in spite of the daily administration of liver extract (fig. 7).

Representative bone marrows at various stages showed a somewhat less definite picture than those obtained with either infection or liver extract alone. In all instances, however, the infection predominated.

The bone marrow of a bird infected on the seventh day of the administration of liver extract and killed four days later is illustrated in figure 8 *A* and *B*. The reticulocyte count at the time of infection was 17.6 per cent, and on the fourth day of infection, at which time the bird appeared acutely ill, it was 3.7 per cent. The bone marrow at that time showed increased cellularity, constituted of both white and red blood cells, and extensive stimulation, with many mitotic figures. It seemed as if the hyperplasia was not so far advanced as in those animals subjected to infection alone, but this may have been due to an individual difference in this animal.

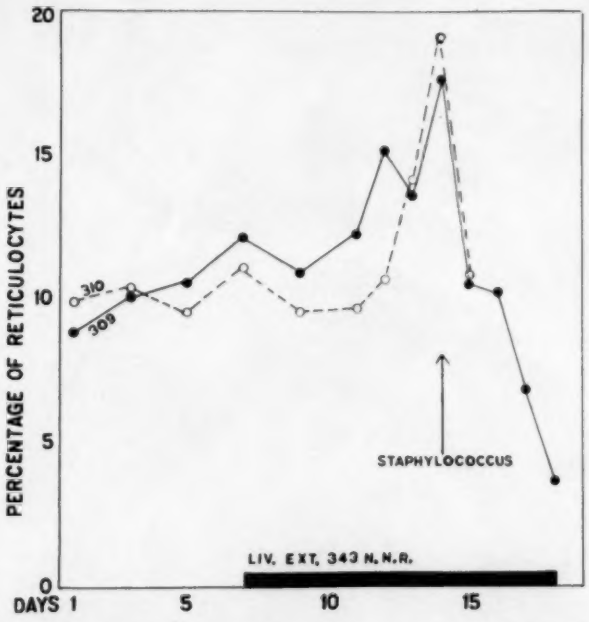

Fig. 7.—Reticulocyte response of two pigeons (309 and 310) to liver extract no. 343 (N. N. R.) and superimposed infection. The reticulocyte response to liver extract was interrupted by the infection, and subsequently the reticulocytes fell below a normal level.

The bone marrow of one of the birds, the reticulocyte counts of which are recorded in figure 1, is illustrated in figure 9. This bird had liver extract for a total of nine days and infection for five days. As may be seen from figure 1, this pigeon had been infected one month earlier and had recovered. It was thought that some resistance to infection might have developed, and therefore a somewhat larger dose of the broth culture was injected (1.5 cc.) the second time. The bone marrow showed intense hyperplasia of white blood cells. The centers of production of red blood cells had not participated to the same extent

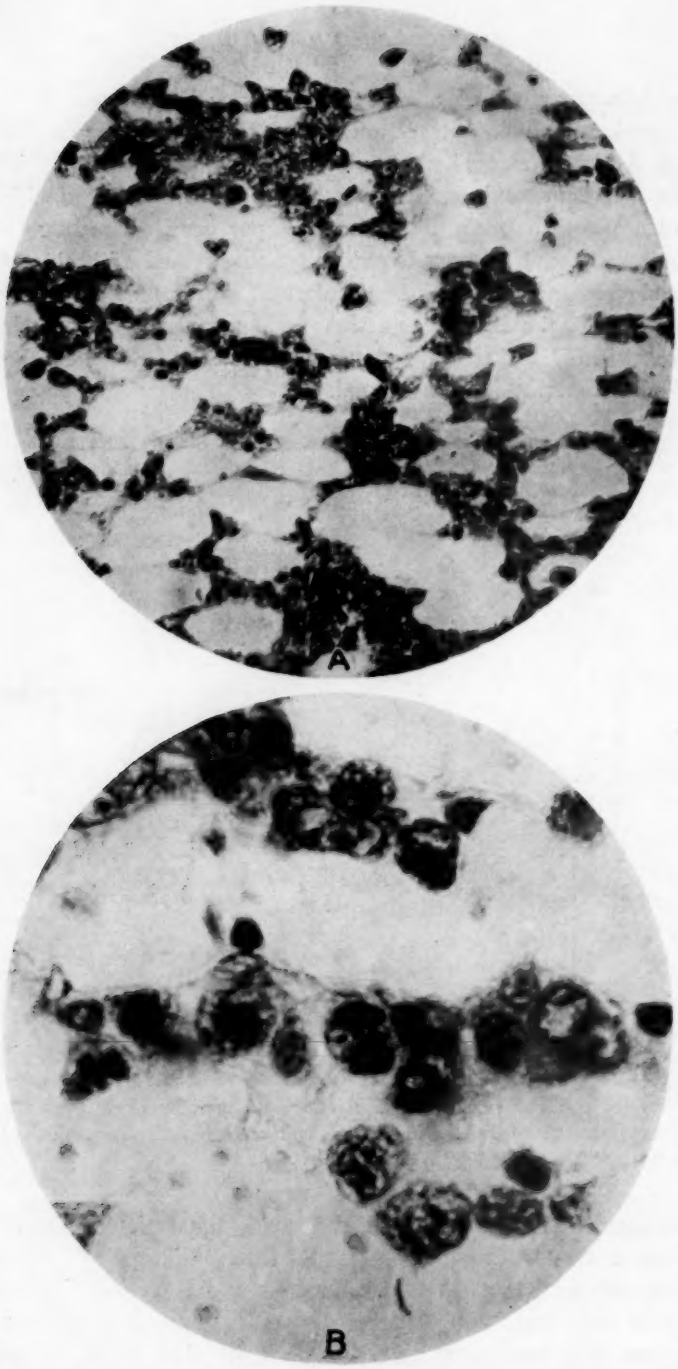

Fig. 8.—Appearance of marrow: *A*, marrow of a pigeon treated with liver extract for seven days, with an infection that had been present for four days. The bird was infected when the reticulocytes were 17.6 per cent. When the bone marrow was obtained the reticulocytes were 3.7 per cent. Active stimulation of both red and white blood cells was present, but this reaction was somewhat less advanced than in animals which had been infected for four days but which had not been given liver extract; × 500. *B*, specimen shown in *A* (× 1,500) showing active mitosis in a row of megaloblasts.

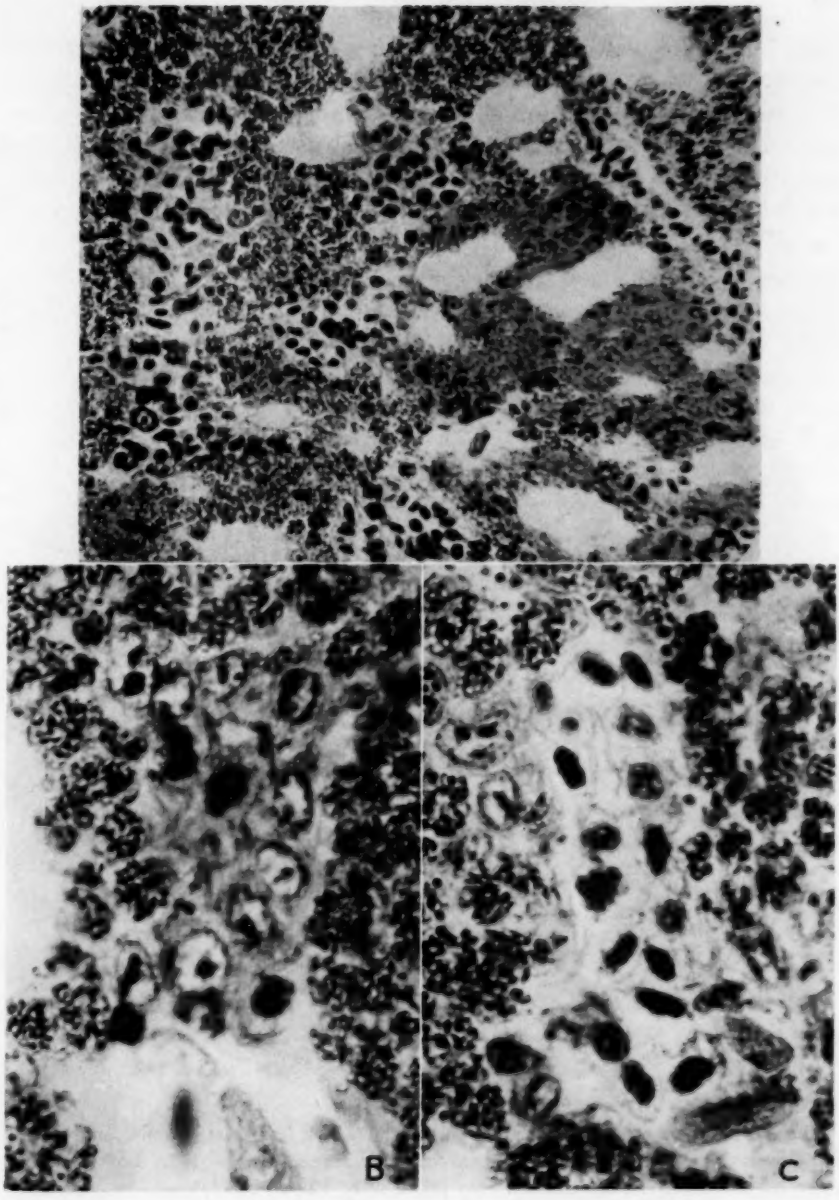

Fig. 9.—Appearance of marrow: *A*, marrow of a pigeon (fig. 1) which had been given liver extract for nine days, and which had been infected for five days. The infection resulted from an injection of 1½ cc. of a broth culture of Staph. aureus. Note the solid hyperplasia mainly of white blood cells with small centers of production of erythrocytes, which consisted of either practically mature cells or young megaloblasts in active mitosis; × 500. *B*, same specimen as shown in *A* (× 1,500). Note the small center of production of megaloblasts with mitotic figures. *C*, same specimen as shown in *A*. Note the center of production of red blood cells consisting mainly of normoblasts shrunk from the edges of the sinusoidal capillary; × 1,500.

(fig. 3 *B*). They were small, containing mainly mature cells, which had shrunk from the edges of the intersinusoidal capillaries, which, as a rule, are lined with megaloblasts. However, here and there were small centers consisting entirely of megaloblasts in active mitosis. It seemed as if two influences had been at work, namely, the liver extract, which had influenced the majority of the red blood cells present before

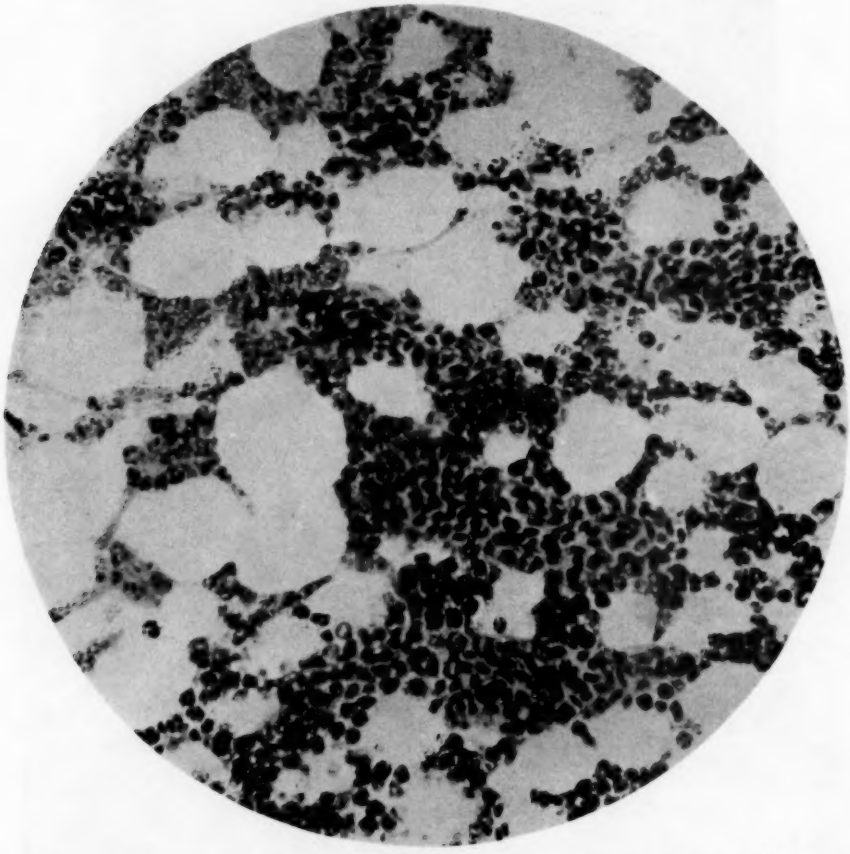

Fig. 10.—Appearance of marrow of a pigeon which had been given liver extract for eleven days, and which had been infected for seven days; × 500. The reticulocytes on the day the bone marrow was taken were 16 per cent.

infection, then the superimposed infection, causing active stimulation of both red and white blood cells. The difference in composition of these foci of red blood cells is illustrated in figure 9, *B* and *C*.

Figure 10 shows the bone marrow of a bird that received liver extract for eleven days and was killed on the seventh day after infection. The reticulocytes in the peripheral blood were just beginning to increase

in number. The stimulation of red blood cells from the infection was prominent, although the erythrocytic foci did not seem to be as large as on the seventh day of infection in birds receiving no liver extract.

To determine whether liver extract influenced the extension of both red and white blood cells in the marrow to any marked extent when infection was superimposed, six birds were selected and matched as to weight and composition of the blood. To three of these animals liver extract was given for ten days; then all the animals were infected with the same culture of Staph. aureus. The pigeons were then put to death in pairs after twenty-four, forty-eight and seventy-two hours. In the birds receiving liver extract, no extension of the centers of production of red blood cells to the radial marrow was noted. The superimposed infection, however, had caused an early stimulation of both red and white blood cells. The reaction in all the birds seemed to be commensurable, as far as could be judged, with the intensity of the infection in each individual animal, regardless of whether the bird had received liver extract or not. The intensity of the infection was judged by the appearance of illness in the bird and the degree of anemia resulting from the infection.

COMMENT

In analyzing the results obtained it is essential to keep in mind that the bone marrow of the pigeon functions on a more immature level than that of many laboratory animals and man. This is reflected in the peripheral blood, where normally all the red blood cells are nucleated and the reticulocytes under the standard laboratory conditions mentioned average from 10 to 12 per cent. The bone marrow likewise contains a considerable number of megaloblasts, the youngest recognizable red blood cells. Also the radial bone marrow in the healthy adult pigeon is mainly fatty, and therefore hyperplasia of this marrow would indicate extension of the blood-forming tissue.

In acute pyogenic infection in pigeons, an increase in the number of leukocytes in the blood and an active stimulation of the white blood cells in the bone marrow were observed in most cases. A few exceptions occurred in which the animal died within forty-eight hours from an overwhelming infection. The reticulocytes of the peripheral blood in pigeons surviving the infection fell to a subnormal level at the height of the infection and later rose to levels above normal. The changes in the bone marrow corresponding to these alterations in the peripheral blood were an active new formation of immature erythrocytes, or megaloblasts, in the intersinusoidal capillaries, and extension of erythropoietic tissue into the radial bone marrow. The early stages of bone marrow growth corresponded to the decline of reticulocytes in the peripheral blood. The erythropoiesis then increased with great rapidity,

and bone marrows obtained after the seventh day of infection contained large islands of erythrocytes with a considerable number of mature cells. This phase of bone marrow activity was reflected in the peripheral blood by an increase in the percentage of reticulocytes, which were of greater immaturity than is customarily seen in the blood of normal pigeons. Consequently, infection caused a stimulation not only of white blood cells but also of red blood cells, the various stages of which could be followed with ease. This reaction of the red blood cells to an infection may be due to a circulating toxin acting directly on the intersinusoidal endothelium. It appeared, however, to be an indirect response to a diminution in the number of circulating red blood cells and in the hemoglobin content caused by increased destruction of blood. That an acute self-limited infection, such as pneumonia in man, may produce the same results is suggested from observations that I have made [8] on the reticulocytes in the peripheral blood.

In correlating the reticulocyte response and the condition of the bone marrow in pigeons after the daily administration of liver extract for some days, a surprising fact, suggested by former work,[9] was confirmed, namely, that the reticulocyte response is not accompanied by a stimulation and extension of the erythropoietic tissue. Rather there is a diminution of the quantity of the megaloblasts therein as well as of total erythropoietic tissue, and, as far as could be judged from counts on stained bone marrow sections, a diminution in mitotic figures. It is also of interest to note that the reticulocytes at the peak of their rise in the peripheral blood after the administration of the principle effective in pernicious anemia rarely exceed 20 per cent in contrast with from 25 to 35 per cent after an acute infection with Staph. aureus in healthy birds. It is evident that the mechanism of these reactions must differ fundamentally. The reticulocyte reaction to the infection is easily explained. Ample evidence of stimulation and new formation of erythropoietic tissue was present in the bone marrows. The mechanism of the reticulocyte response to the liver extract is, however, not so obvious. The logical conclusion seems to be that liver extract influences only a megaloblastic marrow and produces a reticulocyte response commensurable with the megaloblastic tissue present, but does not cause a stimulation or extension of erythropoietic tissue. The average percentage of the reticulocytes, 20 per cent, at the peak of their rise in pigeons after the administration of the principle effective in pernicious anemia may indicate that in the normal bird there is an average amount of megaloblasts, or immature cells, that undergo simul-

8. Muller, G. L.: Unpublished observations.

9. Muller, G. L.: Am. J. Physiol. **82**:269, 1927.

taneous metamorphosis. A normoblastic marrow is thus produced in pigeons, a type of bone marrow that probably is abnormal for this animal.

The same reaction that has been observed in pigeons after the administration of the principle effective in pernicious anemia occurs also in man when megaloblastic hyperplasia is present, with regard to both the reticulocytes and the histologic character of the bone marrow. The reticulocyte response obtained in patients with pernicious anemia varies indirectly with the level of the red blood cells, which is apparently proportional to the megaloblastic tissue present. Peabody [10] admirably demonstrated that, in cases of pernicious anemia, the bone marrow, as a result of adequate liver therapy, returns toward normal. This consists in a qualitative change from a dominantly megaloblastic tissue to a dominantly normoblastic bone marrow, the functionally efficient type in adult man. There also occurs a quantitative decrease of the active bone marrow.

It has been suggested by Wright and Arthur [11] that this metamorphosis of the megaloblastic marrow removes a retarding influence on the multiplication of the primitive erythroblast, resulting in more frequent divisions of this particular type of cell. The experimental results in pigeons as well as the therapeutic results in man show a simultaneous metamorphosis of the megaloblasts (primitive erythroblasts), but this is accompanied by few or no signs of activity in the endothelium of the intersinusoidal capillaries of the pigeon's erythropoietic tissue. Nor does the microscopic picture of the bone marrow of patients with pernicious anemia in various stages of remission indicate that there is an increased activity in primitive cells. Rather the activity of the primitive erythropoietic tissue in pigeons is definitely decreased, at least temporarily.

With the conception of the two altogether different reactions produced in the bone marrow by infection and the principle effective in pernicious anemia, the inhibitory effect of infection on the action of the potent principle in pernicious anemia becomes explainable. It may be seen from the experiments recorded here, in which the influence of infection was superimposed on that of liver extract, that in practically every instance the reaction to the infection was the predominating feature, although, as was to be expected, the results were of two types. The interruption and prevention of a reticulocyte rise in response to liver extract by an acute infection were repeatedly demonstrated, with a subsequent larger reticulocyte response after the infection had subsided than could be ascribed to liver extract alone. This might be

10. Peabody, F. W.: Am. J. Path. **3**:179, 1927.
11. Wright, G. P., and Arthur, B.: J. Path. & Bact. **33**:1017, 1930.

ascribed to an increase of the megaloblastic tissue caused by the infection. The identical interruption of a reticulocyte rise by acute cystitis in a patient with pernicious anemia and the subsequent rise to a higher level after the infection had subsided have been recently reported by Smithburn and Zerfas.[12]

It therefore seems probable that the inhibitory effect of infection on the action of the principle effective in pernicious anemia is due to the enormously increased activity of the primitive cells of the erythropoietic tissues resulting from infection, which liver extract in ordinary doses is unable to control. Apparently, acute infection produces temporarily a bone marrow of the megaloblastic type, the type that seemingly can be transformed into a normoblastic marrow in uncomplicated pernicious anemia and in normal pigeons by the addition of the principle effective in pernicious anemia. One may perhaps speak of the principle effective in pernicious anemia as a controlling substance that is either lacking or present in insufficient amounts in patients with pernicious anemia, and present in pigeons in small amounts proportional to other substances favoring a megaloblastic type of bone marrow.

SUMMARY

Experiments on pigeons dealing with the influence on the reticulocytes and the bone marrow of an acute infection, liver extract no. 343 (N. N. R.) and acute infection induced during the administration of liver extract have been described.

Intramuscular administration of broth cultures of Staph. aureus produced an initial fall of reticulocytes in the peripheral blood, followed by a rise above the normal level. The bone marrow showed active stimulation and extension of both red and white blood cells. The phase of decreased number of reticulocytes in the peripheral blood corresponded to rapid growth and division of immature red blood cells in the bone marrow.

The oral administration daily of liver extract for short periods also produced a reticulocyte response. The bone marrow, however, was quantitatively reduced and qualitatively changed from a marrow with many megaloblasts, or primitive young red blood cells, to a late erythroblastic and normoblastic marrow with a diminution of mitotic figures.

Infection superimposed after and during the feeding of liver extract caused a decrease in the number of reticulocytes in the peripheral blood comparable to that found in birds with infection only. Reticulocyte responses to liver extract were interrupted. The bone marrow showed a mixed picture in which the response to liver extract was distinguishable from that to infection, with the latter reaction predominating.

12. Smithburn, K. C., and Zerfas, L. G.: Ann. Int. Med. **4**:1108, 1931.

The underlying mechanism of the action on the bone marrow of substances effective in pernicious anemia was found to be diametrically opposite to the influence of infection. Liver extract transformed a megaloblastic bone marrow to a more mature level, while acute infection stimulated the primitive cells, or the endothelial cells of the intersinusoidal capillaries, to active new formation of megaloblasts. The neutralizing effect of infection on the action of substances effective in pernicious anemia thus seems explainable.

The reticulocyte response, the bone marrow changes and the influence of infection as observed in patients with pernicious anemia after the administration of potent material have been produced experimentally in pigeons, an animal peculiarly sensitive to substances effective in pernicious anemia.

FIBROMYOMA OF THE BREAST

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In a recent discussion of benign tumors of the breast, Kleinschmidt [1] differentiates sharply between those of the nipple and skin and those of the breast proper. In the first group are hemangioma, fibroma, lipoma and rarely myoma. In the second group are adenoma, fibro-adenoma and fibroma, but not myoma.

Ten cases of leiomyoma of the nipple have been reported by Virchow,[2] Sokolow,[3] Niklas,[4] Riegel,[5] Hiebaum,[6] Bland-Sutton,[7] Bauer,[8] Kaufmann,[9] and Driak and Sternberg.[10] Reviews by Lindfors,[11] Lieber,[12] Schauder [13] and Driak and Sternberg [10] cover these cases. Bauer [8] studied the anatomy of the smooth muscle of the nipple that gives rise to these tumors.

Does myoma of the breast proper occur? Recent books on mammary tumors or on tumors in general do not mention it (Cheatle and Cutler,[14] Ewing [15]). A few cases have been reported, however, which deserve analysis. Klob [16] in 1864 mentioned two cases of what he called fibroma; an occasional muscle fiber was seen here and there. It is not clear whether in these cases the tumor was of the breast proper, since

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3. Sokolow: Virchows Arch. f. path. Anat. **58**:316, 1873.
4. Niklas: Inaug. Diss., Würzburg, 1889.
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6. Hiebaum, A.: Prag. med. Wchnschr. **20**:314, 1895.
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15. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1931.
16. Klob, J. M.: Pathologische Anatomie der weiblichen Sexualorganen, Vienna, W. Braumüller, 1864, p. 492.

there is no description or report. Ribbert [17] mentioned a case, but also with no description or report. Ribbert also cited a case reported by Abramow.[18] This, however, proved to be an adenomyoma. Schauder [13] recently reported a case, but from the description and photomicrograph it is undoubtedly a sarcoma. Driak and Sternberg are essentially in accord with these conclusions. It appears that Kleinschmidt was apparently correct in excluding myoma from the benign tumors of the breast.

Unfortunately these authors did not have access to a case reported by Strong.[19] His case is an exception in that it is one of myoma of the breast proper, and in its clinical, gross and microscopic features resembles the following case in every detail.

REPORT OF A CASE

A 45 year old white woman entered the Cook County Hospital on March 2, 1932, with the complaint of a lump in the right breast. This lump had been present for fifteen years, had been painless, and was only very slowly getting larger. About two months before her admission to the hospital, the lump became painful and began to enlarge more rapidly. There had been no discharge or bleeding from the nipple. The patient had been pregnant several times, but had always aborted before one or two months. For the last eighteen months she had been having menstrual irregularity.

On physical examination, the lower half of the right breast was found to be occupied by a large, firm tumor mass the size of a small grapefruit. The tumor was independent of the nipple. The overlying skin was slightly discolored. There was no axillary or supraclavicular adenopathy; there were no other findings of significance.

The impression then was of a carcinoma of the breast. At operation, a simple mastectomy was done, including the breast, the nipple and the tumor mass, and the specimen was sent to the laboratory for a rapid frozen section. This revealed a benign fibromyoma, and no further resection was done. The patient made an uneventful recovery and went home on the seventeenth postoperative day.

The breast tissue was almost entirely replaced by the tumor, which was very firm but slightly elastic, well encapsulated, and entirely distinct from the nipple, the margin being 2 cm. from the nipple (fig. 1). The cut surface was grayish white and trabeculated. Near the center was an irregular cystic area, 2 by 2 by 3 cm. in dimensions, filled with blood-tinted fluid. The tissue at the margin of this cystic area was edematous and mottled with deep red areas.

Frozen and paraffin sections from nine different areas of the tumor stained by hemalum-eosin, van Gieson's stain and Mallory's phosphotungstic acid hematoxylin method revealed the tumor to be composed of smooth muscle cells arranged in interweaving bundles separated by a moderate amount of connective tissue (fig. 2 *A*). There was a tendency toward perivascular foci of proliferation. In some areas this was pronounced, the muscular wall of the blood vessels blending indistinguishably into the surrounding concentrically arranged tumor tissue (fig. 2 *B*). The cells stained yellow by van Gieson's stain and purple-blue by the

17. Ribbert, M. W. H.: Geschwülstlehre, Bonn, F. Cohen, 1914, vol. 9, p. 427.
18. Abramow, S. S.: Zentralbl. f. allg. Path. u. path. Anat. **12**:926, 1901.
19. Strong, L. W.: Am. J. Obst. & Gynec. **68**:53, 1913.

Mallory method; the connective tissue stained red by both methods. The nuclei were fusiform, with rounded ends, distinct nuclear membrane, and fine evenly distributed chromatin granules. There was no anaplasia. Very few mitotic figures were seen. The Mallory method brought out the fine intracellular myofibrils characteristic of mature smooth muscle cells. No glandular elements could be found. In the region of the cystic area various degenerative changes could be followed. Thrombosis of numerous blood vessels was seen. This was followed by atrophy and necrosis of many of the muscle fibers and small areas of hemorrhage. There was then an overgrowth of connective tissue which became

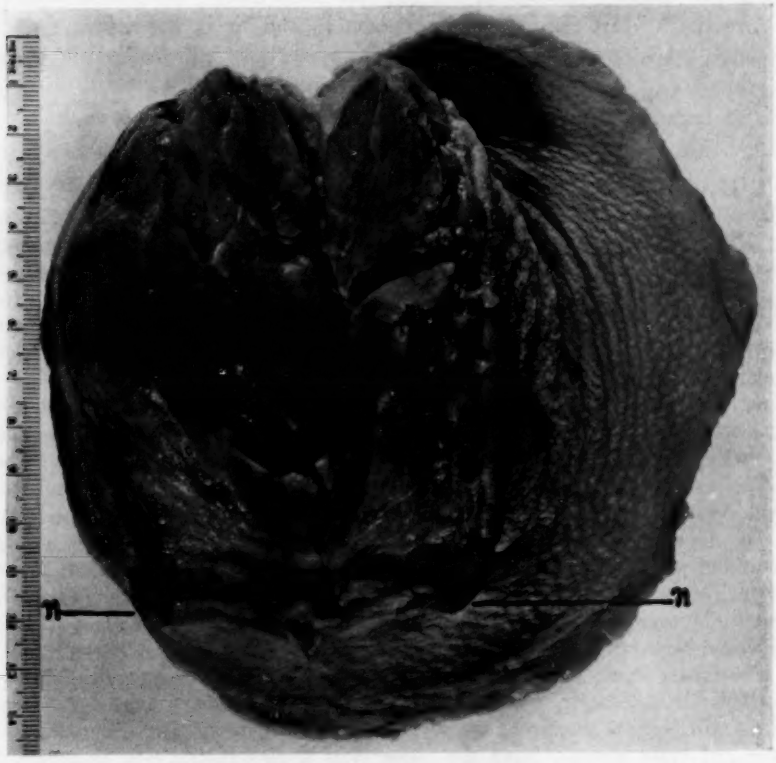

Fig. 1.—Fibromyoma of the breast. The nipple (*n*) has been cut through; its separation from the tumor is distinct.

edematous and loosened. Small cystic areas developed, which finally fused together to form the central cystic cavity. Diagnosis: Fibromyoma of the breast with cystic degeneration.

COMMENT

The histogenesis of this tumor is of interest. There are four possibilities.

It may be teratoid in origin, with extreme overgrowth of the myomatous element. The pseudomucinous cystadenoma of the ovary and the struma ovarii are such tumors; occasionally in teratoma of the testis

and in mixed tumors of the salivary glands one element predominates. Chondroma and similar tumors of the breast are considered to be of teratoid origin, and this tumor may be of similar nature.

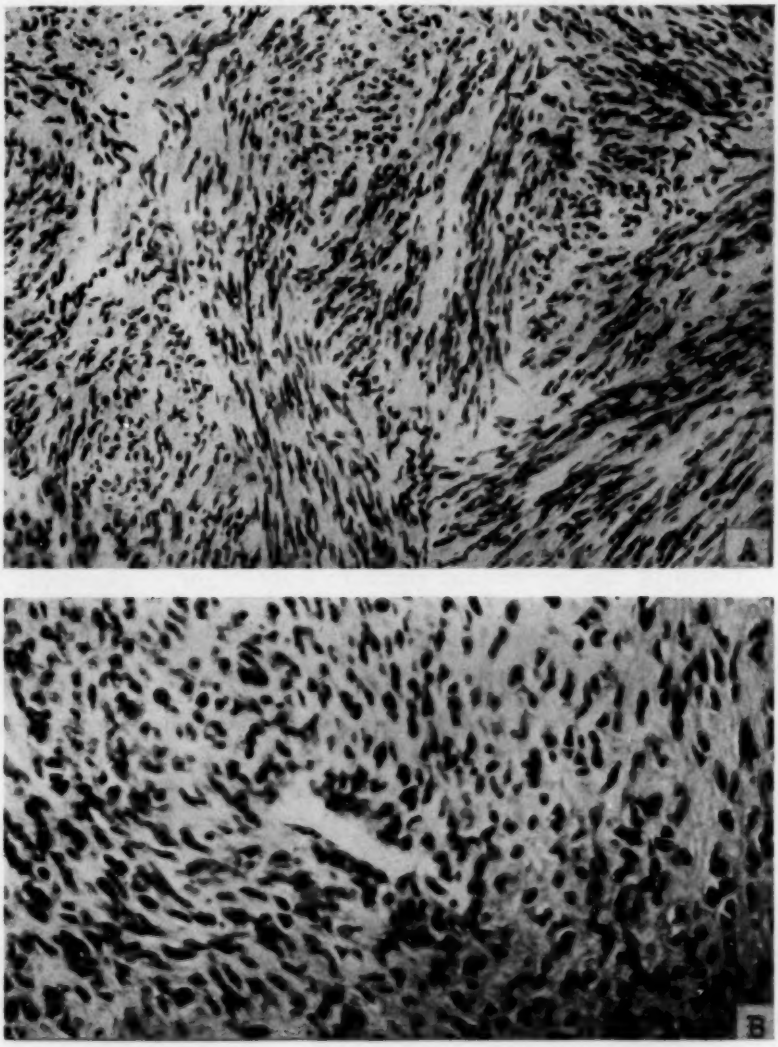

Fig. 2.—Fibromyoma of the breast. *A*, interweaving bundles of smooth muscle cells; no anaplasia and no mitotic figures; Hemalum-eosin. *B*, fusion of the muscular wall of the blood vessel with the surrounding tumor tissue; van Gieson's stain.

A second possibility would be embryologically displaced smooth muscle from the nipple. Fibro-adenoma of the breast has been con-

sidered to be the result of embryologic defects; a similar explanation may apply here.

A third theoretical possibility is the "myo-epithelial layer" of the French school of Peyron, Corsy and Surmont.[20] The sweat glands have an incomplete layer of smooth muscle applied against the epithelium, which seems to regulate secretion. From embryologic data these workers correlate this muscle layer with the outermost of the two layers of epithelium lining the ducts of the breast. They are able to recognize tumors arising from this layer, which are frequent in animals but occur occasionally in the human being. This conception is at the present time still in a theoretical stage.

A fourth possibility appears to be the most logical: an origin from the muscular layer of the blood vessels. The perivascular foci of proliferation and the fusion of the muscular layer of the blood vessels with the tumor tissue speak in favor of this. Strong's case had a marked similarity in this respect.

SUMMARY

A case of fibromyoma of the breast is reported. This is a true fibromyoma, having no glandular elements, and is of the breast proper, having no relation to the nipple. One similar case has previously been reported. The histogenesis offers four possibilities: teratoid origin with overgrowth of the myomatous element; embryologic displacement of smooth muscle from the nipple; an origin from the "myo-epithelial layer" of the French school, and that from the muscular layer of the blood vessels. The last is apparently the true source of the tumor.

20. Peyron, A.; Corsy, F., and Surmont, J.: Bull. Assoc. franç. p. l'étude du cancer **15**:21, 1926; Compt. rend. Soc. de biol. **94**:90, 1926.

TUBEROUS SCLEROSIS

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Tuberous sclerosis is a rare congenital, sometimes hereditary and familial disease of unknown etiology, characterized by mental deficiency, epilepsy, tumors of various tissues, developmental defects and a histologically distinctive lesion of the brain which may involve any lobe, any surface or any folium and is often associated with glial masses that hang in the ventricles like "candle gutterings." It occurs uncommonly in the United States, more frequently in Australia [1] and Great Britain, and is confined largely to Europeans,[2] especially those of the poorer classes.[3] Syphilis,[4] tuberculosis and neuropathic tendencies [5] have been noted in the parents in a number of cases. The persons with this disease almost always show mental impairment, which occasionally may be so slight that it goes unrecognized. Psychically, they may be normal [6] and later regress, but are usually imbeciles or idiots from birth. Epilepsy generally begins in infancy, although it may not appear for a number of years, when it is apt to precipitate the onset of the final phase. The attacks increase in frequency and duration in the later stages, varying considerably in their clinical characteristics,[7] simulating at times idiopathic [8] or jacksonian [9] epilepsy. Death may occur in status epilepticus, or postepileptic mania may follow.[2] Other nervous symptoms are rare.[10] Delay in talking, walking and dentition are the rule, and various stigmas of degeneration have been recognized, of which the high narrow palate is perhaps the most common. Optic atrophy, cata-

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This work was aided by a grant from the Martin Research Fund.

From the Pathological Department of the Jefferson Medical College and Hospital, the Pathological Department of the Philadelphia General Hospital and the Pediatric Department of the Jefferson Medical College and Hospital.

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9. Greig, D. M.: Edinburgh M. J. **28**:105, 1922.
10. Fowler, J. S., and Dickson, W. E. C.: Lancet **1**:1351, 1910.

ract and retinal tumor (the so-called phakoma) are occasionally the only clinical manifestations.[11] The cerebral and cerebellar lesions consist of pearly white, gray or yellowish-gray, hard nodules; these may be no larger than a pea, or they may involve half of a hemisphere. They are well defined, principally confined to the surface, and they cause atrophy of adjacent gyri. Associated with them are concretions, cystic cavities, glial or vascular tumors and meningitis. Microscopically, the altered glial cells and astrocytes make a dense fibrillar network, which surrounds peculiar giant cells, interrupts the cyto-architecture of the cortical layers and imparts a notable density to the hypertrophic cortical nodule. There are agenesis of myelin sheaths and persistence of the external granular layer of the cerebral cortex. Cutaneous lesions arise about the nasolabial folds or elsewhere on the face, although seldom below the clavicles;[12] they consist of fibroma-like nodules of the Hallopeau-Leredde type, simple adenomas of sebaceous glands[13] or altered hair follicles.[14] The tumors associated with this condition, found in the brain, ependyma, kidneys, heart, skin, pancreas, intestine, thyroid gland and mammae, may be undifferentiated embryonic neoplasms, gliomas, hemangiomas, lipomas, myomas, fibromas, mixed tumors, teratomas, dermoid cysts or carcinosarcomatodes. The disease is uniformly fatal. Without an autopsy it is often unrecognized or incorrectly diagnosed. Early descriptions were made by von Recklinghausen,[15] Virchow[16] and Bourneville.[17] Subsequently Sherlock[18] proposed the name epiloia, which has been taken up and used extensively by the British. Important contributions have been made by Bundschup,[19] Freeman,[20] Bielschowsky,[21] Babonneix,[22] Bolsi,[23] Kreyenberg, Delbanco and Haack,[24] Lazar,[25] Globus[26] and Turville.[27]

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REPORT OF CASES

CASE 1.—R. C., a 4 months old Negro girl, weighing 8 pounds (3,600 Gm.), was admitted to the Philadelphia General Hospital on March 31, 1927, in the service of Dr. C. A. Fife. The father and mother were living and well. The mother had had three pregnancies, one of which terminated in abortion, and the other two in normal deliveries. The first child, a girl, died of pneumonia at the age of 1 year. The second failed to gain weight, but was otherwise apparently healthy until the night before admission, when she was seized with a severe convulsion, followed by rigidity, tremor and fever. On examination, she presented the physical signs of bronchopneumonia, craniotabes, bulging of the fontanels, twitching of the eyes and spasticity of the muscles. The pupils were equal and in middilation, but did not react to light or to accommodation. For two months, convulsions recurred frequently. The child failed to gain weight, was fretful, sensitive, refused to nurse, vomited frequently and perspired copiously, and her breathing was accompanied by a peculiar snorting sound. For a brief interval in June, 1927, some improvement was noted; nursing was resumed, convulsive seizures abated, and muscular rigidity largely disappeared. On relapse, all the previous symptoms returned with increased severity. Suffering from inanition, the patient contracted pneumonia and died on Jan. 24, 1928.

The afternoon temperature ranged between 101 and 102 F., rising to 105 F. with each attack of pneumonia; the pulse rate was from 120 to 160; the respirations, from 30 to 50.

The spinal fluid showed a pressure of 12 millimeters of mercury, 2 cells per cubic millimeter, a faint trace of globulin, a negative Wassermann reaction and a colloidal gold curve of 0.0111000000. The blood sugar was 0.80 Gm.; the blood urea, 37 Gm. The white blood cells numbered 12,600, polymorphonuclear leukocytes 57, lymphocytes 40 and monocytes 3. The urine was normal.

The clinical diagnosis was: congenital syphilis, tetany, bronchopneumonia and possibly syphilitic or tuberculous meningitis.

The therapy included administration of mercury, iodides and sulpharsphenamine, spinal drainages and exposures to ultraviolet rays.

Postmortem examination (Dr. R. B. Richardson) showed extreme emaciation; marked plantar flexion of the fingers and toes; exfoliation, scarring and depigmentation of the skin along the right nasolabial fold; along the left, numerous small, flat, closely set nodules; eruption of two normal upper and lower incisors; a normal condition of the scalp and meninges, and no enlargement of the brain. On palpation of the brain, nodules were located that projected slightly beyond the surface. They were sharply demarcated, with slightly roughened surfaces, and were of a rubber-like consistency. They occupied symmetrical positions in the mesial borders of the rolandic areas and the posterior portions of the frontal lobes, extending over the convex and down into the mesial surfaces. The dimensions of the nodule in the right cerebral hemisphere were 3 by 5 cm., and that in the left, 2.5 by 4 cm. The convex surface and to a less extent the bases of the affected convolutions were broadened (fig. 1 *A*). When incised, the nodules did not settle away from the knife as normal cerebral tissue does. The cortex was pale, mottled and imperfectly defined. The uninvolved gyri adjacent to the sclerotic ones were pink and atrophic, with shallow fissures. All the cerebellar folia were widened, and on palpation their consistency was identical with that of the cerebral nodules. The pons, medulla, pituitary gland, basal vessels and ventricles appeared normal. There was bilateral bronchopneumonia; the left suprarenal gland was twice as large as the right; all the mesenteric lymph nodes were enlarged; the thymus was small; the heart, aorta, spleen, liver and kidneys were normal.

CASE 2.—S. O., a white girl, was born in December, 1929. The father, mother and two older brothers were living and well. The mother's gestations and accouchements were normal. The day after birth the infant twitched continuously and appeared to be in a "trance." Convulsions lasting from three seconds to one hour began on the fifth day and recurred at frequent intervals. Following these, she would lie on the right side and alternately sleep forty-eight hours and remain awake fifteen hours. Her appetite, manner of eating and gain in weight were normal. She was taken to a hospital on Feb. 25, 1930. Her family physician stated that the convulsions were on the left side, and that on lumbar puncture bloody fluid had been withdrawn. While she was in the hospital, all the convulsions were on the right side. The right side of the face was involved, the head and eyes were drawn to the right, and it seemed that the right extremities, particularly the arm, were involved, and that both the right arm and leg were more spastic. Because of these discrepancies the child was closely observed for five days before active measures were taken. On repeated examinations the findings remained constant, and a decompression on the left side seemed indicated. This revealed no changes other than an overdistended subarachnoid space, from which a rather abnormal amount of fluid was obtained. The recovery was uncomplicated, and following the operation convulsions were less frequent. They were still on the right side. The child was discharged on March 19, 1930, with the suggestion that, after complete recovery from the effects of the operation, she should be returned for a right subtemporal decompression. It was noted (March 29) that the circumference of the head was 1 inch (2.5 cm.) greater than it had been prior to operation. Since developing hydrocephalus was suspected, it was thought wise not to operate. Two months later she was admitted to Jefferson Hospital. Her head was uniformly enlarged, the eyes moved continuously and independently of each other, and when disturbed the muscles became rigid. Vomiting occurred occasionally, but food was usually retained. Generalized rigidity was frequent and alternated with marked flaccidity and listlessness. On occasion, a typical hydrocephalic cry was heard. The chest, abdomen and reflexes were apparently normal, and the lymph nodes were not palpable. On June 29, 1930, signs of infection developed with fever (107 F.) and Cheyne-Stokes respirations. Death occurred two weeks later.

On roentgenographic examination of the brain, the soft parts appeared retracted near the anterior fontanel on the left side and in the region of the vault and occiput. Ventriculographic examination showed dilatation of the lateral ventricles but a perfectly free communication with the other ventricles. Roentgenographic examination of the spine and skull following injection of iodized poppy seed oil 40 per cent showed the ventricular system enlarged, although the third and fourth ventricles were not well isolated.

The hemoglobin content was 65 per cent; the red blood cells numbered 3,780,000; the white blood cells, 5,400. The color index was 0.98. The polymorphonuclears were 21; the small mononuclears, 72; the large mononuclears, 7. The spinal fluid was clear and contained 1 cell per cubic millimeter. The globulin was not increased; sugar was 32 mg. The Wassermann reaction was negative.

At postmortem examination, except for well marked lividity and rigidity, the trunk, limbs, skin, hair and genital organs were normal; the cranial incision appeared well healed. The skull was uniformly and proportionately enlarged. The right anterior half of the skull cap showed craniotabes, and adherent to it was a thickened, gray, tough, opaque dura. Considerable fluid had accumulated beneath the unadherent and unthickened pia. The brain weighed 790 Gm., and the entire anterior half of the right cerebral hemisphere was uniformly pale and hard. The

transition from pink uninvolved cerebral tissue to the sclerotic area was abruptly marked by extreme anemia and a cartilaginous consistency. These hard, anemic convolutions were broad, superficial and in some places umbilicated. They cut with increased resistance and on section presented a sharp edge and a pale, broad, dull, somewhat mottled, porous, poorly marked surface. The adjacent gyri were deformed and partially atrophied. The lateral ventricles were markedly dilated, chiefly in their posterior horns. There were no ventricular obstructions or tumors. The ependyma, pons, medulla, cerebellum, pituitary gland, basal vessels and third and fourth ventricles appeared to be normal. Permission to examine the contents of the chest and abdomen was not obtained.

Microscopic Observations in Cases 1 and 2.—Cerebral and cerebellar tissues in each case were fixed in alcohol, formaldehyde, Zenker's fluid and Müller's fluid. Some were frozen and sectioned; others were blocked in paraffin and celloidin, cut, and stained with phosphotungstic acid, Nissl's toluidine blue, scarlet red, hematoxylin and eosin, Weigert's stain for myelin, Bielschowsky's silver stain, Cajal's silver stain for neuroglia, Gram's stain for bacteria in tissues and Levaditi's stain for spirochetes.

The histologic features in the two brains were identical.

With Weigert's stain, myelinization was, of course, nowhere so abundant as in an adult brain. In the sclerotic patches it was practically absent (fig. 1 *A*). The silver preparations demonstrated that this was not due to absence of nerve fibers. There were loss of architecture, marked gliosis of the marginal layers and a lack of the sharp line of cleavage from underlying cortical layers (fig. 1 *B*). Neurofibrils were greatly increased and tended to form in clumps. Irregular and abnormal ganglion cells were present in the upper layers of the cortex and in the overlying marginal layers.

Sections prepared by Cajal's silver stain for neuroglia (fig. 1 *C* and *D*) showed enormous overgrowth of neuroglia, which formed a matted, interlacing network of fibers that extended through the granular layer upward into the subarachnoid space. Grouped directly beneath the space were collections of ganglion cells.

Along with the loss of architecture in the toluidine blue (Nissl) preparations (fig. 2 *A*) there was a resemblance to the deeper layers of the cortex in dementia paralytica. Neuroglia was increased, the number of ganglion cells was reduced, rod cells were present in great numbers, and small blood vessels were unduly prominent. In size and shape, the degenerated and necrotic ganglion cells varied considerably and, with their atypical dendrons, pointed in every direction.

In the sections stained with scarlet red, enormous quantities of lipoid were demonstrated in practically every cell. Phagocytes loaded with fat droplets were grouped about blood and lymph vessels, and many monster cells were seen loaded with lipoid material. In figure 2 *B*, one of these can be seen at the left of the center, and others, in the upper left hand corner. Neurofibrils from the granular layer extended into the subarachnoid space.

In the Bielschowsky preparations, the cytologic and morphologic variations were well brought out. In figure 2 *C*, a "large cell" with its processes is located just below the marginal layer and resembles the Betz cell of the motor cortex. An abundance of neurofibrils and atypical ganglion cells occupied the marginal layer, the boundaries of which were indistinct. The increased number and length of the cell processes made it difficult to demonstrate with any frequency or degree of accuracy the cytologic and fibrillar relationship. The differences in staining of the nuclei, protoplasm and processes of the "large cells" whereby neuroglial elements can be distinguished from ganglion cells were noted in a high percentage. Bolsi claimed to have demonstrated this much better with a modification of the silver nitrate pyridinate method of Cajal.

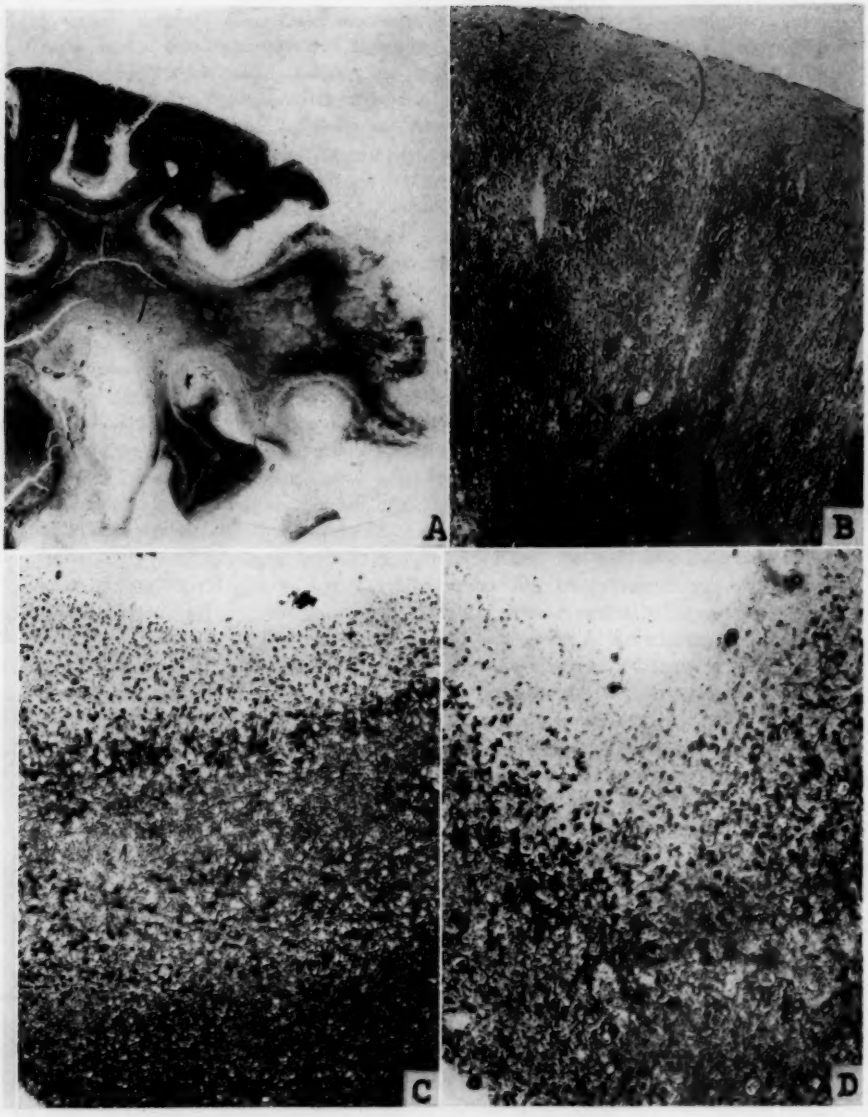

Fig. 1.—*A*, section showing hypertrophic and uninvolved gyri. The mottled appearance of the sclerotic patch on the right is characteristic of the lesion. It shades off into the normal convolutions on the left. Myelin sheath stain. *B*, section through a sclerotic patch, showing agenesis of myelin sheaths, loss of architecture and marked gliosis. Myelin sheath stain. *C*, section through a sclerotic patch, showing intense laminar gliosis. Silver stain for neuroglia (Cajal). *D*, same as *C* under higher magnification.

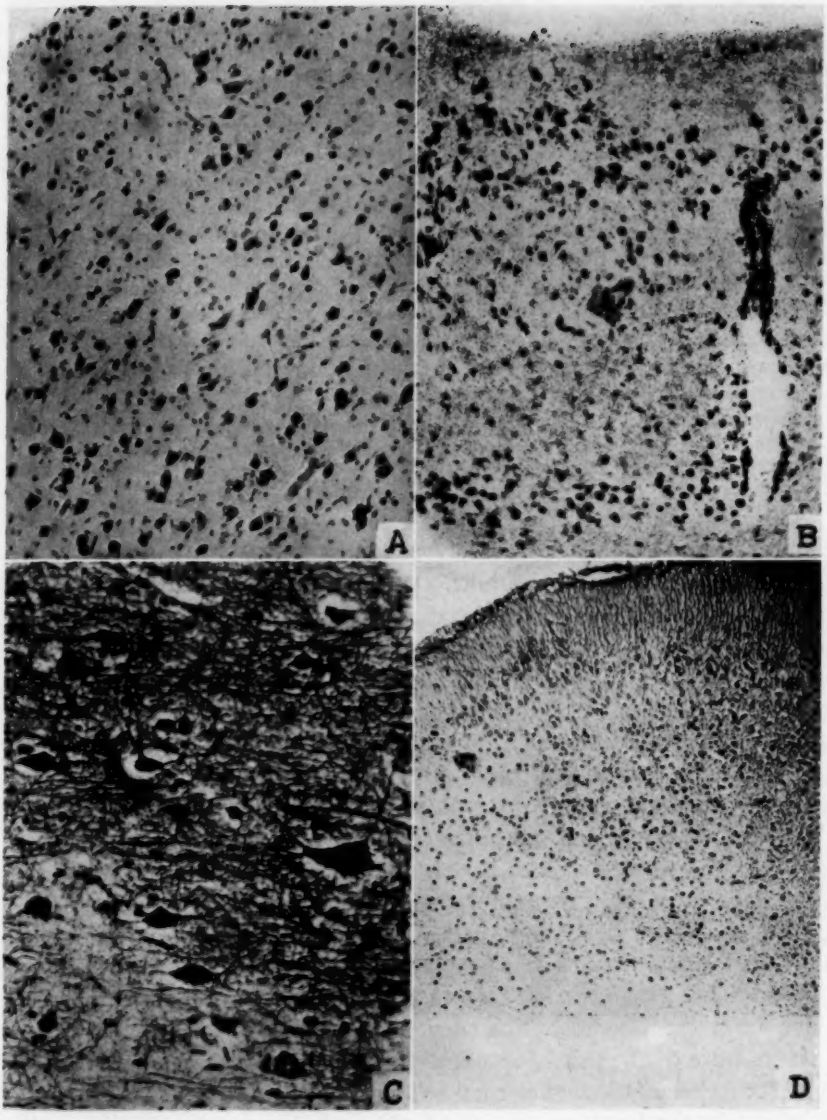

Fig. 2.—*A*, section through a cortical sclerotic patch just below the marginal layer. Note the resemblance to the deeper cortical layers in a person with dementia paralytica. Toluidine blue (Nissl stain). *B*, section through a hypertrophic convolution. Note the enormous quantities of lipoid, droplets of which can be seen in practically every cell. They can be better seen by magnifying the photograph with a hand lens. Fat-containing phagocytic cells are concentrated about a blood vessel to the right of the center. Scarlet red stain. *C*, cortex of hypertrophic convolution, showing part of marginal layer and upper cortical layers. Bielschowsky preparation. *D*, cerebellum, case 1. Note the gliosis of the molecular layer and the paucity of nerve cells in the granular layer. Except for the two wrinkled and distorted cells, the Purkinje cells are absent. Phosphotungstic acid stain.

The cerebellar sections in case 1 consisted entirely of areas of tuberous sclerosis, characterized by widened folia, concretions, sometimes partially or entirely calcified arteries, capillaries with proliferated endothelium and an atrophic molecular layer of varying thickness (fig. 2*D*). The latter was the seat of an intense, irregular gliosis, which formed a brushlike arrangement on the surface. Just proximal to this, a band of parallel fibers frequently began and stopped abruptly. No normal Purkinje cells were found. In their places were a few large, irregular, oval or polyhedral, more or less indistinct cells, which had shrunk away from the spaces they appeared previously to have occupied. Their nuclei were either absent, irregular, pyknotic or fragmented with increased chromatin granulation. Most of these cells were devoid of processes, but a few short, coarse, rudimentary ones were found. The cytoplasm stained poorly and contained irregular granules and small vacuoles. Identical cells were found in ectopic positions in the granular and medullary layers. The small round, deeply staining cells of which the granular layer is normally largely composed were found only sparsely in the affected areas. In their stead was a dense infiltration by cells indistinguishable from embryonic glial elements. They were scattered sparsely throughout the molecular and granular layers and were usually arranged perpendicular to the surface.

COMMENT

A family history of syphilis, tuberculosis, degenerative or neuropathic tendencies was not elicited in either case. The parents were below the age of 30 and seemed normal. The Wassermann reactions in both cases were negative, and none of the lesions characteristic of congenital syphilis or of tuberculosis was found. Since adenoma sebaceum is said to be much rarer in races other than the Caucasian, it is interesting that it was present in a Negro infant (case 1). The sebaceous glands, already present in the fetus, begin to secrete about the fourth year,[28] and adenoma sebaceum usually does not appear earlier, although it has been noted at 9 weeks,[29] 6 months [3] and in our case at 13 months. Except for the adenomas of the sebaceous glands, no tumors (limited autopsy, case 2), no stigmas of degeneration and no skin lesions such as fibroma molluscum, pedunculated polypi, pigmented nevi, "café au lait" spots or anemic or valvular nevi, which have been described by Yakovlev and Guthrie,[30] were noted. Both infants were of the third gestation, and both were girls. The gestations and accouchements were normal. There was no evidence of tuberous sclerosis in the brothers or sisters, although in case 1 only a guarded statement can be made. The course in both was characterized by a steadily progressive mental and physical deterioration, expedited by inanition and terminated by infection. There was no evidence of retinal tumors, of contractures or of visual or auditory impairment. Interest-

28. Caylor, H. D.: Ann. Surg. **82**:164, 1925.

29. Weech, A. A.: Am. J. Dis. Child. **37**:766, 1929.

30. Yakovlev, P. I., and Guthrie, R. H.: Arch. Neurol. & Psychiat. **26**:1145, 1931.

ing ocular signs and craniotabes were noted in both cases. Copious perspiration, vomiting and interference with feeding were noted in case 1. Both infants suffered from epilepsy, and in one (case 2) the localizing signs were sufficient to justify surgical intervention. The shifting of the signs, which at first was attributed to discrepant statements, may be explained thus: The lesion was in the right hemisphere, and the original signs pointed to that area; with the advent of hydrocephalus and compression of the opposite side, the localizing signs shifted to the other side. The same phenomenon is often observed in cases of tumor of the brain.

As has been observed by others,[31] surgical intervention appeared not to influence the subsequent course.

As death occurred while both patients were still infants, the histologic changes in the lesions were not far advanced as judged by the absence of tumors and by the absence (case 2) and paucity (case 1) of concretions. In case 1, the calcific deposits were confined to the cerebellum, which coincides with the observation that when widespread they are apt to be more plentiful in that region. It was there, also, that two prominent characteristics of tuberous sclerosis were represented, viz., the glioblastomatous and the neurocytodysgenetic.[21] Enlargement of the brain, hydrocephalus and dural thickening were noted in case 2. The hydrocephalus was chiefly confined to the lateral ventricles and could not be accounted for on an obstructive basis, since the ventricular communication was intact. In some cases it has been ascribed to tumors that may be widespread although occurring commonly in the ventricles, the caudate nucleus and the stria terminalis. It is interesting in this connection that Freeman [20] was not convinced that any causal relationship existed in his case between the ventricular hydrocephalus and a tumor that lay adjacent to the foramen of Monro. Cysts have been found in the occipital lobe away from the sclerotic lesions or occasionally in the frontal lobe in the midst of a tuberous area. They were not definite in either of our cases, although in case 2 the porous nature of the cortex suggested them. In case 2, the entire anterior half of the right cerebral hemisphere was converted into an area of tuberous sclerosis, and the altered histologic picture extended well down into the fissures, which is uncommon.[32] In case 1, the cerebral nodules were small, but the rare cerebellar lesion was so extensive that definitely normal structure was not encountered. In case 1, the left suprarenal gland was twice as large as the right. It is unfortunate that the restrictions on the autopsy in case 2 prevent a more positive statement regarding visceral tumors. Clinically, there was no evidence of them, but, as Hyman [33] has shown, they may exist unrecognized.

31. Volland: Ztschr. f. d. ges. Neurol. u. Psychiat. **74**:505, 1922.
32. Pellizzi, G. B.: Ann. di freniat. **10**:326, 1901.
33. Hyman, A.: J. Urol. **8**:317, 1922.

ETIOLOGY

Bourneville,[17] Fürstner and Stuhlinger [34] and Brushfield and Wyatt [2] believed tuberous sclerosis to be an inflammatory lesion. In some cases, the parents have been tuberculous or syphilitic,[4] and in a few cases the Wassermann reaction of the blood has been positive. Campbell [35] considered it an evolutionary disturbance, beginning not before the seventh fetal month, which is the time at which the plan of the sulci and gyri is laid down. Vogt,[36] Globus,[26] Bielschowsky [21] and Hartdegen [37] regarded it as a malformation, a blastoma or an inseparable combination of the two, and attributed the inflammatory changes to alterations taking place in the areas of tuberous sclerosis. Bielschowsky especially emphasized these combined manifestations and stressed the probable interrelationship of syringomyelia, solitary gliomas and von Recklinghausen's disease (peripheral spongioblastosis) with tuberous sclerosis (central spongioblastosis). Yakovlev and Guthrie pointed out further clinical analogies with von Recklinghausen's disease, cerebral angiomatosis and vascular nevi of the skin, suggesting that these were ectoblastic malformations to be classified under the term "congenital ectodermoses" along with the congenital ectodermal dystrophies [38] and dysplasias.[29]

A striking feature of tuberous sclerosis is manifested in the lipoferous tissue disturbances. Scattered through the sclerosed nodules and grouped about blood and lymphatic vessels are large phagocytic and monster cells loaded with lipoid droplets. In every case there is agenesis of myelin sheaths, and in many there are adenomas of sebaceous glands, renal and mammary lipomas, dermoid cysts and lesions of the suprarenal glands consisting of atrophy and aplasia of the cortical cells, fibrosis of the medulla or, as in case 1, hypertrophy of one and atrophy of the other gland. These changes suggest an embryologic metabolic imbalance, and this opinion is further supported by the work of Steinbiss [39] in his studies of rhabdomyoma of the myocardium. Theorizing along this line seems inappropriate at this time. Pathologic data assembled so far in this condition point so strongly to a metabolic imbalance that metabolic studies and administration of the suprarenal cortical hormone,[40] as a trial, seem warranted.

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34. Fürstner and Stuhlinger, cited by Lind.[1]

35. Campbell, A. W.: Brain **28**:367, 1905.

36. Vogt, H.: Ztschr. f. d. Erforsch. u. Behandl. d. jugendl. Schwachsinns **2**:1, 1908.

37. Hartdegen, A.: Arch. f. Psychiat. **11**:117, 1880.

38. Clouston, H. R.: Canad. M. A. J. **21**:18, 1929.

39. Steinbiss: Virchows Arch. f. path. Anat. **213**:22, 1923.

40. Swingle, W. W., and Pfiffner, J. J.: Am. J. Physiol. **96**:164, 1931.

SUMMARY

The clinical and pathologic features of two cases of tuberous sclerosis are presented and discussed. One of the cases, which was complicated by adenoma sebaceum, occurred in a Negro infant.

In obscure cases of obstructive or nonobstructive hydrocephalus associated with epilepsy with or without adenoma sebaceum, tuberous sclerosis must be considered as a possibility.

The features of lipodystrophy are emphasized, and it is suggested that tuberous sclerosis is a congenital metabolic disturbance.

BLOOD CYSTS ON THE HEART VALVES OF NEW-BORN INFANTS

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Small, circumscribed, elevated nodules on the heart valves of newborn infants were reported as early as 1844 by Elsässer [1] and 1857 by Luschka.[2] Since then many similar observations have been recorded, but very few in other than the German or the French medical literature. There has been considerable controversy as to the nature of these nodules, first one view predominating, then another as later studies superseded earlier ones.

INCIDENCE

Elsässer [1] found the nodules in more than half of infants examined between birth and the twenty-third day of life. Luschka [2] reported a 25 per cent incidence. Parrot [3] considered the nodules as an almost invariable finding, reporting their occurrence in 103 of 120 infants examined post mortem in the first few months of life. In Fahr's [4] series of infants in the first few months of life, the nodules occurred almost constantly; in those in the second half of the first year, the incidence diminished to 50 per cent, and in those past the first year, the nodules occurred rarely. Haushalter and Thiry,[5] Wegelin [6] and Jonsson [7] cited an incidence of, respectively, 78 per cent, 66 per cent and 63 per cent. While the greatest frequency of occurrence is in the very first few months of infancy, a number of cases occurring in childhood and adult life have been reported—namely, by Haushalter and Thiry,[5] Bundschuh [8] and Wegelin.[6]

From the Department of Pathology, University of Illinois College of Medicine.

1. Elsässer, cited by Luschka.[2]
2. Luschka, H.: Virchows Arch. f. path. Anat. **4**:171, 1852; **11**:144, 1857.
3. Parrot, M. G.: Arch. de physiol. norm. et path. **1**:538, 1874.
4. Fahr, E.: Virchows Arch. f. path. Anat. **184**:274, 1906.
5. Haushalter, P., and Thiry, C.: Arch. de méd. expér. et d'anat. path. **10**: 558, 1898.
6. Wegelin, C.: Frankfurt. Ztschr. f. Path. **2**:411, 1908; **9**:97, 1912.
7. Jonsson, S.: Virchows Arch. f. path. Anat. **222**:345, 1916.
8. Bundschuh, E.: Frankfurt. Ztschr. f. Path. **6**:65, 1911.

The valves of predilection for the distribution of the blood cysts are the mitral and the tricuspid, on which the nodules occur with about equal frequency. They are found less often on the pulmonic, and infrequently on the aortic, leaflets. Wegelin [6] recorded the following distribution: On the mitral valve alone the nodules were found ten times; on the tricuspid valve alone, six times; on the mitral and the tricuspid valves, thirteen times, and on the tricuspid and the pulmonic valves, one time.

Jonsson [7] described nodules in forty-five of seventy-one cases in which postmortem examination was performed. The distribution of nodules on the various valves is recorded in the table.

In sixteen consecutive postmortem examinations of infants (the premature as well as the full-term, and the stillborn as well as those born

Distribution of Nodules on the Heart Valves in Jonsson's Series of New-Born Infants

	Valves Showing Nodules	Number of Cases
Mitral, tricuspid, pulmonic and aortic	4	2
Mitral, tricuspid and pulmonic	3	2
Mitral and tricuspid	2	23
Tricuspid and pulmonic	2	1
Tricuspid and aortic	2	1
Mitral and aortic	2	1
Mitral	1	7
Tricuspid	1	6
Aortic	1	1
Pulmonic	1	1
Total		45

living) twelve showed blood cysts on the valves. A similar high incidence is recorded in the various published reports.

We have seen, on the leaflets of the heart valves of new-born infants, small, circumscribed, elevated, dark red nodules. These elevations appear grossly to be small cysts filled with blood. When present, they are almost invariably seen on both the mitral and the tricuspid leaflets, infrequently on the pulmonic leaflets and rarely on the aortic. The nodules occur as elevated, circumscribed, spheroid globules, presenting a dark red color, and varying from pinpoint to pinhead in size, seldom exceeding 1 mm. in diameter (fig. 1). They vary in number from two or three to ten or fifteen, though as many as thirty have been reported. The nodules project above the auricular surface of the auriculoventricular leaflets near the free margin, between the edge and the line of contact on closure. On the semilunar leaflets, the nodules project into the ventricle and are located at or very close to the line of attachment of the leaflet.

HISTOLOGIC DISCUSSION

On histologic examination, the nodules as seen in cross-section appear as monolocular or bilocular or even multilocular spaces filled with red blood cells (fig. 2). The partitions dividing the spaces into several chambers are not constantly complete, thus there is obvious communication between compartments. The spaces are lined by a single layer of endothelial cells, in appearance similar to the surface endothelium of the valve leaflets. The cells are flattened and show well staining,

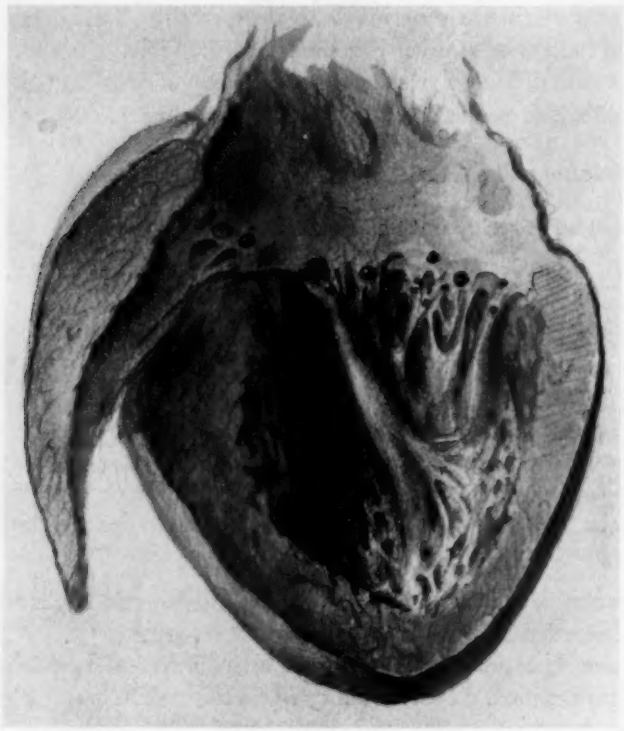

Fig. 1.—A heart showing blood cysts on the mitral valve, on the auricular surface near the junction of the chordae tendineae with the leaflet; × 2.

elongated nuclei. The spaces present the appearance of cystlike enlargements protruding above the surface level of the leaflet. The projecting surface of the nodule and the corresponding side of the leaflet present a smooth, uniformly even outline except for the elevation of the nodule above the surface level, while the opposite side is irregular and uneven, showing numerous indentations of the surface endothelium into the stroma of the leaflet. The stroma is a moderately cellular, young, fibrous connective tissue, which shows no differentiation into special layers. The partitions dividing the blood-filled spaces

into several chambers are composed of stroma similar to that of the valves. Near the attachment of the valve to the myocardium a few blood vessels are inconstantly seen, though in the body of the leaflet no blood vessels are found (fig. 3).

ORIGIN

When we come to a consideration of the genesis of the nodules, we find a variety of opinions. Essentially there have been four expla-

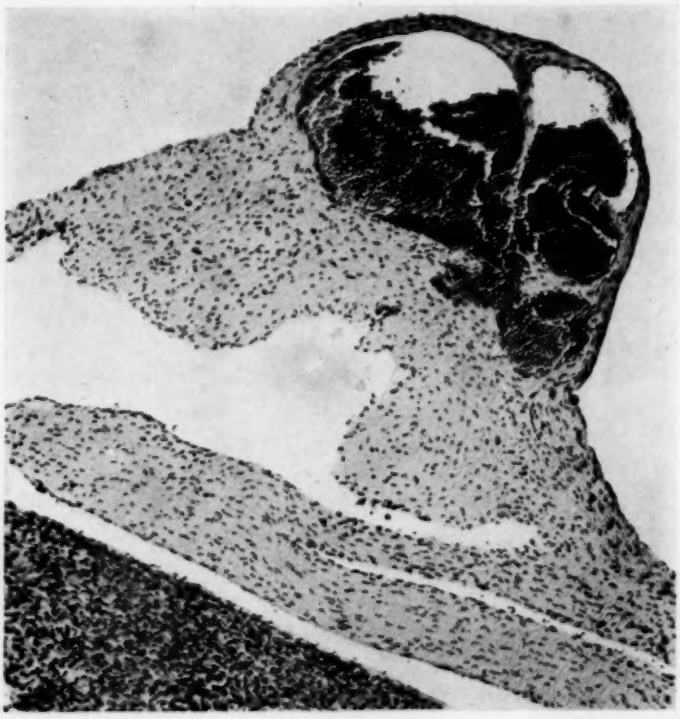

Fig. 2.—A microscopic section of a mitral valve, showing a blood cyst divided by a partition and filled with blood cells; hemalum and eosin stain; × 40.

nations, each with minor modifications propounded by different observers:

1. The blood cysts represent extravasations of blood, namely, hematomas.

2. The cysts represent ectatic or dilated blood vessels.

3. The cysts represent angiomas.

4. The cysts are spaces filled with blood as a result of the pressure of blood into crevices running from the surface of the leaflet into the stroma forming the leaflet.

At first the nodules on the valve leaflets were considered as extravasations of blood, or hematomas. Elsässer in 1844 spoke of the extravasations. Luschka [2] cited Elsässer, and described the nodules, predominantly occurring on the auriculoventricular leaflets near to the free edge, as small extravasations of blood into the so-called nodules of Albini. Luschka assumed that the blood vessels which he was able to demonstrate were the source of the extravasations. Parrot [3] reported the occurrence of the blood nodules in 103 of 120 cases in which post-

Fig. 3.—A microscopic section of the same mitral valve as shown in figure 2, showing, in addition, endothelium-lined clefts extending into the stroma of the leaflet; hemalum and eosin stain; × 40.

mortem examination was performed, and explained the origin of the nodules as the result of rupture of the vessels of the leaflets, and spoke of blood nodules rather than extravasations. Contrary to Luschka, who considered the extravasations as occurring into the nodules of Albini, Parrot believed that the blood nodules gave rise to the nodules of Albini. Von Kahlden [9] also adhered to the view that the hematomas on the valves represented bleeding into the connective tissue composing the

9. von Kahlden, C.: Beitr. z. path. Anat. u. z. allg. Path. **21**:288, 1897.

nodules of Albini. In this first explanation a mechanical traumatic factor was believed to be the significant initiating agent, with diapedesis or rhexis leading to the development of the hematomas.

The next view sought to emphasize vascular ectasias or varicosity as representing the essential feature of these nodules. Berti [10] emphasized that these nodules were blood-filled spaces lined by endothelium. He also noted that the nodules were not seen before the seventh month of intra-uterine life, and that they apparently disappeared after the fifth month of extra-uterine life. He explained the origin of the nodules as follows: In the vessels of the valves there is a gradually developing involutionary process which is accompanied by the proliferation of elastic tissue from the base to the margin, giving rise to constrictions and ectasias. Fahr [4] (with minor modifications) subscribed to the views of Berti, considering the nodules as vascular ectasias. By accepting the idea of vascular ectasia, both authors presupposed vessels to the valves. Fahr stated that vessels are found in early infancy and less frequently or not at all in adulthood. They occur more often in the auriculoventricular leaflets and hardly ever in the semilunar leaflets. Fahr, however, differed from Berti in considering the vascular regression as directly related to the disappearance rather than to the formation of the ectasias. He believed that the ectasias disappeared as a result of the progressive occlusion of the vascular network. As in the previously outlined explanation, mechanical traumatic moments were considered of significance.

While the view generally accepted was in the process of development, Nichols [11] reported the case of an infant with these blood cysts on the valves, and spoke of them as angiomas. This view was never extensively held and does not accord fully with all the facts demonstrated and recorded by the various observers. The cysts are neither newly formed blood vessels nor even dilatations of previously existing vessels.

The view now most widely acknowledged was developed in part by Haushalter and Thiry. They explained the origin of the blood-filled saccules as the result of the pressing of blood into small canals and emissaries by back pressure as a result of increased tension incidental to crying and exertion. The direction of the back pressure is toward the auricles. These canals that Haushalter and Thiry speak of have their origin at the marginal and submarginal insertion of the chordae tendineae into the leaflets of the valve on the ventricular surface. They found none of these nodules in stillborn infants, and considered this fact as confirmatory evidence in support of their view. Luschka,[2]

10. Berti, G.: München. med. Wchnschr. **45**:1194, 1898.

11. Nichols, J. L.: J. Exper. Med. **10**:368, 1908.

Berti,[12] Fahr [4] and others, however, found these nodules in stillborn infants from the sixth intra-uterine month to full term. Subsequent studies by various authors, however, led to amplification, some modification, and support of the ideas developed by Haushalter and Thiry.[5]

Thus Meinhardt [13] presented a report confirmatory in many respects of that of Haushalter and Thiry. He found that the auriculoventricular leaflets in the new-born infant are composed of a delicately meshed fibrous connective tissue stroma, rich in cells, indicative of the fact that active proliferation is yet taking place. The connective tissue fibers are delicate and without dominant arrangement into bands running in special directions. Furthermore, when one examines the mitral and tricuspid leaflets, the auricular side is uniformly smooth, but on the ventricular side the chordae tendineae lead to unevenness, clefts and indentations, lined by endothelium, leading into the valve substance. These clefts are not entirely simple, for they may divide, or give rise to ampulla-like dilatations. With systole blood is pressed into the clefts, and in diastole the blood flows out again, except when the blood is pressed into the narrower canals or into canals extending deep into the stroma of the leaflets. Thus are formed the cysts lined by the endothelium of the valve surface. In the case of the semilunar valves there are slight differences, but the principle is identical as outlined for the auriculoventricular valves. In the floor of the sinus of Valsalva, also, clefts enter into the substance of the leaflet and extend toward the ventricle. With the closure of the valves blood is pressed back into the sinus of Valsalva and into the clefts.

Wegelin [6] presented essentially the same observations as Meinhardt and Haushalter and Thiry. He stated that the pressure of blood into the endothelium-lined clefts by stretching and dilatation gives rise to cysts. The projection of the auriculoventricular nodules above the surface of the leaflet into the auricle and of the semilunar valve nodules into the ventricle was explained by the direction of the clefts and of the forces. By adhesion of the endothelium the clefts are closed, thus starting the process of obliteration of the canals which, when open, connect the lumen of the heart with the cysts. The canal being closed, the blood in the cyst becomes converted into a hyaline mass, and connective tissue ingrowth then completes the physiologic regression. The rarity of deeper indentations, their relatively infrequent occurrence, and the absence of chordae tendineae account for the lesser number of nodules in the leaflets of the semilunar valves. In older age the clefts are present, though in lesser number. Then, the valve tissue is denser and more resistant, hence the fact that the nodules are so rare in the adult

12. Berti, G.: Arch. f. Kinderh. **31**:371, 1901.
13. Meinhardt, H.: Virchows Arch. f. path. Anat. **192**:521, 1908.

Bundschuh [8] further corroborated the work of Wegelin and the others holding similar views.

Jonsson [7] published a lengthy study confirmatory of the observations of Haushalter and Thiry, Wegelin, Meinhardt, Bundschuh and Hammes,[14] though disagreeing with the latter in speaking of the clefts as "vessels to the valve." Jonsson explained the monolocular cyst as a development from the multilocular cyst by thinning out and atrophy and eventual disappearance of the partitions as a result of the dilatation of the cyst. There are transitions. The monolocular cysts frequently contain rests of septums as small islets or as narrow bridges of tissue, identical with the stroma of the leaflet and lined by endothelium. Jonsson concluded that the clefts in the valve leaflets are to be considered as structurally analogous to the other irregular depressions in the inner surface of the heart. The cysts develop when blood is pressed into those spaces or potential spaces. That cysts develop depends on the specific structure of the leaflet as well as on the character of the tissue of the leaflet. In these studies of Jonsson and Wegelin reconstructions were used to demonstrate the connection of the cysts with the lumen of the heart.

Apparently there is no pathologic significance to these nodules. They are rather to be considered as a common anatomic finding.

SUMMARY

Blood-filled cysts, appearing as small, circumscribed, dark red, elevated nodules, are found on the valve leaflets of new-born infants.

The nodules are frequently found between the seventh month of intra-uterine life and the fifth month of extra-uterine life. In our series of infants the incidence was 75 per cent. After the first half year of life the frequency decreases to become a rarity after 2 years of age.

Four views relating to the genesis of the nodules are presented and discussed: 1. The nodules represent hematomas or extravasations of blood. 2. The nodules represent vascular ectasias. 3. The nodules represent angiomas. 4. The nodules represent endothelium-lined clefts into which blood is pressed and in which by dilatation cysts are formed. The last view is supported by wax reconstructions as well as by analysis of the demonstrable facts.

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14. Hammes, F.: Virchows Arch. f. path. Anat. **193**:238, 1908.

PHEOCHROMOCYTOMA OF THE SUPRARENAL MEDULLA (PARAGANGLIOMA)

A CLINICOPATHOLOGIC STUDY

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Our purposes in this article are to collect all the recorded cases of pheochromocytoma of the suprarenal gland; to present the salient clinical and pathologic features of all these cases, and to attempt to reduce them to a common denominator, i. e., to present their clinicopathologic cross-section; and to report the fifth case of malignant pheochromocytoma of the suprarenal gland, one that is associated with another primary malignant growth (of the thyroid gland) and an unusual blood picture.

In many respects, the suprarenal glands are the most interesting organs in the body. Although they were discovered by Eustachius in 1563, their structure remained a mystery for over three hundred years, until von Kölliker described them histologically and until the first embryologic studies appeared in 1886.

So far as their physiology is concerned, although the early work of Vulpian, Czibulski and Szymonowicz, of Oliver and Schafer, of von Fuerth and particularly of Abel culminated in the brilliant isolation of epinephrine by Takamine, much is still unknown. While it is established that the medulla produces epinephrine, Hartman demonstrated the presence of the latter in the cortex as well, so that it is possible that, in addition to being "the most essential regulatory organ for cholesterin-fat metabolism" (Aschoff) and having something to do with secondary sexual characteristics, the cortex may be concerned in the production of epinephrine. We may say only that the suprarenal glands produce epinephrine, and that the suprarenal cortex is essential to life.

Of the greatest significance for the study of the tumors of the suprarenal glands, particularly those of the medulla, are the embryologic considerations, of which the most important is the fact that the suprarenal cortex and the medulla are practically two distinct and separate organs (as they are anatomically in the fish). While the anlage of the cortex

begins from coelomic epithelium, the first anlage of the medulla is formed by the migration of the sympathetic primitive cells (sympathogonia), which is usually complete when the embryo has reached the length of 85 mm. From the sympathetic primitive cells are developed the pheochromoblasts, and from these the mature medullary cells, or the pheochromocytes, which are large, polyhedral cells, each with a finely granular cytoplasm and a round vesicular nucleus, usually eccentric, containing nucleoli.

It is only natural, then, that dissimilar in their embryology, unlike in their histology and different in their physiology, the suprarenal cortex and the medulla give rise to tumors that are as distinct from each other as would be those of two different organs, pathologically just as much as clinically.

For a clearer understanding of the tumors of the medulla of the suprarenal gland, one must, therefore, remember that in the medulla three different types of tumors may arise, depending on the types of the cells from which they originate: (1) sympathogonioma (sympathoblastoma, neuroblastoma or neurocytoma), tumors derived from the embryonic sympathogonia; (2) ganglioneuroma, tumors derived from the mature ganglion cells, and (3) pheochromocytoma (chromaffin cell tumor, paraganglioma), tumors originating from mature pheochromocytes.

Since we are concerned only with the last-mentioned tumors, we must mention another general consideration concerning them before we pass to a thorough study of their pathologic and clinical manifestations: It is the question of the so-called chromaffin system. It was Kohn (1902) who suggested that this is a tissue system, pointing out that the cells of the so-called paraganglions—the carotid gland, the abdominal collection of cells and the so-called organ of Zuckerkandl (found at the bifurcation of the aorta, especially in children)—closely resemble the cells of the medulla of the suprarenal gland, not only in their morphology, but also in giving the so-called chromaffin reaction, i. e., the deposit of brown granules in the cells when the tissues are fixed in fluids containing potassium bichromate (owing to the fact that the latter, under the influence of epinephrine, is reduced to insoluble peroxide of chromium). Kohn (according to Bailey and Miller) also stressed the fact that paraganglions have a common embryonic origin with the medulla of the suprarenal gland, while Fulk and MacLeod furnished evidence that the active principle of the retroperitoneal chromaffin tissues has the same physiologic action as epinephrine. However, Maximow, pointing out that cells similar to the chromaffin tissue cells are also found in the kidney, liver, testis and heart, questioned the advisability of speaking of the "chromaffin system" and of including the medulla of the suprarenal gland in this system until "it has been shown that all of the chromaffin

organs have the same internal secretion," since "the assumption that the paraganglia elaborate epinephrine, just like the chromaffin cells of the medulla of the suprarenal, has not been securely established."

GENERAL FEATURES OF PHEOCHROMOCYTOMA

The first mention of this tumor is credited to Perley about 1890, although a case was mentioned by Fränkel in 1886. The first description is credited to Manasse in 1893. Fifty-three cases have been reported, all of which are tabulated elsewhere in this article.

Pheochromocytoma occurs in animals (Stilling; Zanfrognini) as well as in man. In the former it is always benign, while in the latter it may be malignant, five undoubted malignant cases having been reported (Bonnamour, Doubrow and Montague; Gravier and Bernheim; Masson; King; Lazarus and Eisenberg) and one doubtful (Masson and Martin). All malignant cases have given widespread metastases.

Incidence as to Age.—Although cases have been reported in which the patients' ages ranged from 2½ to 82 years, the fifth decade of life is the one of greatest frequency of cases (about 30 per cent), with the fourth decade next (about 20 per cent). Three of the malignant cases occurred in patients 30, 47 and 68 years of age; the ages of the patients in the remaining two malignant cases are not known.

Incidence as to Sex.—The early impression that the tumor is much more prevalent among women than among men (according to Rabin, the ratio is three to one) is entirely erroneous. Of the forty-eight cases in which the sex of the patient was recorded, twenty-five occurred in women and twenty-three in men. Of the five malignant cases, two occurred in men and one in a woman; the sex of the other two patients is unknown.

Distribution and Location.—The question whether it is possible and advantageous to speak of the chromaffin system has been discussed; but regardless of the acceptance or nonacceptance of this concept, it must be admitted that pheochromocytoma not only occurs in locations other than the suprarenal glands, but is much more frequent in locations outside these glands, there being, according to Rabin, about eighty cases of pheochromocytoma of the carotid gland and three cases involving the organ of Zuckerkandl (Handschin; Hausmann and Getzowa; Stangl), one case of the retroperitoneal chromaffin tissue (Mayo) and one case of sacrococcygeal tissue (Alezais and Peyron).

As to the side on which the tumor occurs, in forty cases in which this information is available, the tumor occurred nineteen times on the right side and thirteen times on the left side, and in eight cases, the tumor was bilateral. All known cases of malignant pheochromocytoma (Alezais and Peyron, 1911) were bilateral.

Association with Other Tumors.—Neurofibromatosis (von Recklinghausen's Disease of the Skin): The following authors presented such combined cases: Herxheimer, Kawashima, Russum and Barry, Suzuki and Zeckwer—five cases in all (9.4 per cent).

Adenoma: Harbitz' patient had a cystadenoma of the pancreas (and a hypernephroma of the left kidney) as well as a pheochromocytoma of the right suprarenal gland. Hedinger's patient had an adenoma of the liver and a colloid adenoma of the thyroid gland, in addition to a pheochromocytoma of the left suprarenal gland.

Malignant Tumors of Other Organs: In one case (the second case of Lazarus and Eisenberg), a malignant pheochromocytoma was associated with a papillary adenocarcinoma of the thyroid gland; in another case (Harbitz), a benign pheochromocytoma was associated with a hypernephroma of the kidney on the opposite side (as well as with a benign cystadenoma of the pancreas).

Wahl's famous case was a combination of pheochromocytoma, ganglioneuroma and neurocytoma.

Association with Hypertension.—This probably is the most important condition coexisting with pheochromocytoma. Of fifty-three cases, twenty-five (47 per cent) showed the association with hypertension, while in six cases no information was recorded. Owing to the lack of clearcut abstracts of histories and necropsy protocols it is difficult to state just what the mutual relationships were. Did hypertension coexist with atherosclerosis? Did either one or the other or both coexist with renal disease? In what cases was hypertension continuous? In what cases was it paroxysmal? Was it present a sufficient number of years previous to the probable origin of the tumor to be definitely regarded as independent of the tumor?

The available data—fairly accurate—seem to give the following answers to these questions: Three patients showed diffuse atherosclerosis without renal disease and, so far as the information is available, without hypertension. Of twenty-five patients with hypertension, six had nephritis, three had diabetes, one was pregnant, and thirteen had pure (?) hypertension. So much for the statistics, but as soon as one attempts to rationalize and explain the available data, one is beset with great difficulties, some of which, in the light of present knowledge, are insurmountable.

To begin with, the first impression one forms from the study of the association of pheochromocytoma with hypertension is that, since it is the chromaffin tissue of the medulla of the suprarenal gland that produces epinephrine, and since epinephrine produces vasoconstriction and, *eo ipso*, hypertension, it is natural to expect that an increase of the chromaffin tissue would bring about hyperadrenalemia and, *pari passu*,

hypertension. This conception of the causal connection between pheochromocytoma of the medulla of the suprarenal gland and hypertension is particularly alluring because pheochromocytomas located elsewhere, (e. g., those arising from the abdominal sympathetic ganglions, the carotid gland, etc.) have also been found to coexist with hypertension, which should be expected *a priori*, since it was pointed out by Fulk and MacLeod in 1916 that the retroperitoneal tissue contains an active principle with the same physiologic action as that of the suprarenal medulla—epinephrine. True, Fulk and MacLeod did not say that the active principle mentioned is epinephrine, but what they said means just that, for it is hardly possible to conceive that two organs of the same embryology and morphology could secrete two different active principles with the same physiologic action.

We now come to our first real difficulty. There have been at least twelve authentic cases of *cortical* tumors (benign and malignant) associated with hypertension (Oppenheimer and Fishberg; Rowntree and Ball). No explanation of such paradoxical findings has as yet been vouchsafed. If neoplasms of the chromaffin tissue (suprarenal and extra suprarenal) cause hypertension because of hyperadrenalemia (to be discussed presently), why should neoplasms of the suprarenal cortex —so different from the medulla embryologically, histologically and physiologically as to be quite properly regarded as a separate organ (as it is lower in the scale of vertebrate life)—cause hypertension? That they were primary cortical tumors is obvious from the fact that they were followed by characteristic changes in the secondary sexual characteristics. Again, in several cases, removal of the tumor led to disappearance of hypertension—*post hoc, ergo propter hoc*. On the other hand, if one considers how relatively frequent are renal hypernephromas, and how infrequent are suprarenal hypernephromas, and particularly, if one asks oneself why the infrequent cortical tumors in the suprarenal gland always cause a marked disturbance in the secondary sexual characteristics and frequently produce hypertension, while the frequent cortical tumors in the kidney do not, one grows perplexed in attempting to shed light on the connection between tumors of the suprarenal cortex and hypertension. Granting that the question why cortical tumors in the suprarenal gland cause hypertension and changes in the secondary sexual characteristics while such tumors in the kidney do not can be answered by stating that the renal hypernephromas are not cortical tumors but renal adenocarcinomas (an opinion subscribed to by many prominent pathologists), how can we explain the causation of hypertension by tumors of the suprarenal cortex if it is the suprarenal medulla that produces epinephrine (assuming, for the sake of the argument, that hypertension depends on hyperadrenalemia)? The fact that we may

be dealing in the case of the cortical tumor with hypertension of different causation from that in the case of tumor of chromaffin tissue—suprarenal and extrasuprarenal—seems to have been observed by Peyron, who pointed out that in the case of the cortical tumor hypertension is usually continuous, while in that of the chromaffin cell tumor hypertension is usually paroxysmal. To this we may add our own observation that in the case of malignant chromaffin cell tumor either hypertension is absent or there is actually hypotension. Peyron thought that the reason why hypertension is paroxysmal in the case of pheochromocytoma is that the intense proliferation and death of chromaffin cells interfere with the regular and complete secretion of epinephrine, and that, as a result of this, many proepinephrine and paraepinephrine particles get into the circulation, and thus, for the time being, there is no hypertension.

Attempts to account for the hypertension associated with cortical tumors are attended with difficulty, even if it is assumed that the suprarenal cortex produces epinephrine (Hartman), because, as Allen stated, "it has not been proved that epinephrine is necessary for the maintenance of normal vascular tone and blood pressure," and thus these attempts are at best few and highly speculative.

When we come to consider the relation of pheochromocytoma to hypertension, we still are confronted with two difficulties, namely, the inability to prove that hypertension is due to hyperadrenalemia, and the inability to demonstrate that hyperadrenalemia exists in such cases.

So far as the relation of hypertension to hyperadrenalemia is concerned, we wish to point out, as Maximow stated, that "it is quite probable that epinephrine never has physiologic function similar to its pharmacological action. . . . It is secreted in very minute quantities and is rapidly destroyed in the blood stream. Another view is that it is only an excretory product of protein metabolism, since it is probably destroyed before it reaches the arterial blood stream."

Stewart stated that "readers who peruse the literature without critical knowledge might easily conclude that epinephrine has a great functional importance. . . . Many writers assume this as self-evident. . . . The most convincing evidence that the epinephrine secretion does not play an indispensable rôle is the fact that the animals in which the epinephrine output has been suppressed . . . remain indefinitely in good health." He also stated that "it is frequently assumed . . . that the chromaffin inclusion of the adrenal medulla plays a rôle in the maintenance of the normal blood pressure. It has been measured in rabbits and dogs . . . before and during removal of the first adrenal, then up to and during removal of the second gland and then on till recovery or death. No change in the blood pressure was found which could be attributed to loss of the adrenals." Allen also

referred to the work of Ingier and Schmorl, who failed "to demonstrate increased amounts of epinephrine in the suprarenal glands of individuals with hypertension." Janeway, Mosenthal and many others regard the theory of hyperadrenalemia as a cause of hypertension as unproved.

The second difficulty referred to—that of the demonstration of hyperadrenalemia in patients with pheochromocytoma—remains insurmountable, since the present methods of estimating epinephrine in the blood are not accurate enough. We are therefore confronted with the fact that in some cases of tumor of the suprarenal cortex and in most of those of tumor of the medulla (as well as in those of tumor of extrasuprarenal chromaffin tissue) there is either paroxysmal-intermittent or continuous hypertension, and that very frequently removal of the tumor is followed by restoration of normal blood pressure. All explanations of any causal relationship between hyperplasia of the chromaffin tissue and hyperadrenalemia and between the latter and hypertension will remain unsettled so long as there is no positive information on the following points: Is epinephrine produced in the suprarenal medulla, in the cortex or in both? Is the active principle of the extrasuprarenal chromaffin tissue identical with epinephrine? Does the physiologic epinephrine in the human body act in the same way as the pharmacologic epinephrine? Does hyperadrenalemia exist in all the cases of pheochromocytoma? Does hyperadrenalemia mean hypertension?

Association with Other Conditions.—Tuberculosis: Five patients with pheochromocytoma suffered from tuberculosis; three of these had pulmonary phthisis, and two, a diffuse infection involving the lungs, intestines and lymph nodes. Manasse gave pulmonary tuberculosis as the cause of death in the case that he reported.

Diabetes: This was present in five cases—Herde's first case and those of Labbé, Tinel and Doumer, Biebl and Wichels, Helly and Schroeder; in one of the five cases, the pancreas was atrophied (Schroeder).

Vasomotor Instability: Six patients showed symptoms of shock; five of these died shortly after minor surgical procedures. Several other patients had attacks of dyspnea, pallor, numbness and, occasionally, unconsciousness.

Miscellaneous: In one case (Riemer), the patient presented an addisonian syndrome, and in another (Laignel-Lavastine and Aubertin) there was melanoderma.

PATHOLOGIC ANATOMY OF PHEOCHROMOCYTOMA OF THE SUPRARENAL MEDULLA

The tumor may be solid or cystic. In the latter case, the tumor is referred to as chromaffin medullary cystic struma. Of the fifty-three cases, eleven were cystic (two bilateral). All these were benign.

The size of the tumor varies from 1 cm. (Suzuki's second case [1909]; Herde's second case, on the right side) to 12.5 cm. (the first case of Lazarus and Eisenberg); several cases in which the tumor was from 9 to 10 cm. in length have been reported by Suzuki (third case, 1909), Hedinger, Oberling and Jung ("the size of a kidney"), Lascagna, Shipley and Schroeder. All the large tumors were benign. Two of the malignant tumors were 5 cm. long (Lazarus and Eisenberg; King). Information as to the length of the other three malignant tumors is not available. Speaking generally, the larger the tumor, the more apt it is to be cystic and hemorrhagic and to contain necrotic areas; for this reason, a large majority of the larger tumors are soft and reddish in appearance, while the smaller ones are pale gray.

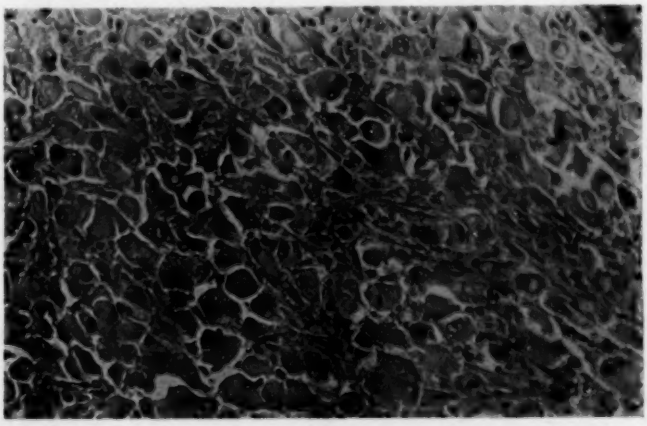

Fig. 1.—Section of malignant pheochromocytoma of the suprarenal medulla, showing the cellularity and the alveolar or trabecular appearance. Note the irregularity in size and shape of the cells. All the photomicrographs were made by A. Plato.

In some few cases, normal medulla could be recognized and was separated from the neoplasm by a distinct, at times very thick capsule, but in most of the cases, especially those of the larger growths, the entire suprarenal gland was converted into a tumor mass which obliterated the medulla but retained a thin, narrow rim of the cortex, usually interrupted at one or more points. At times, the solid part of the tumor occupies the central part of the mass, like the core of a hypernephroma, with multiple cystic areas all around it.

PATHOLOGIC HISTOLOGY OF PHEOCHROMOCYTOMA

The neoplasm (fig. 1) is very cellular and in many places has a slightly or definitely alveolar or trabecular appearance, depending on

the amount of the connective tissue stroma, which varies a great deal in different sections, but is always quite vascular, and envelops the cords of cells on all sides. Even with the lowest magnification, one is immediately struck with the extreme anisocytosis: not only are there occasional cells smaller than erythrocytes and others more than twice as large as neutrophil leukocytes, but less striking differences in size are so frequent and widespread that one's impression is almost kaleidoscopic, for it seems as though there are no two cells of the same size. This feature becomes the more striking the greater the magnification. The great majority of the cells are large, about from 30 to 35 microns long. In form, most of the cells are polyhedral, oval or irregularly trapezoid. At times, one sees a cell strongly resembling the histiocyte as seen in blood films, an ovoid cell, from 50 to 75 microns long, with a very pale cytoplasm and a centrally placed, dark round nucleus, about 20 microns long, containing many nucleoli.

The cytoplasm of most of the cells is abundant and is very finely granular, although a dull, homogeneous appearance is not at all lacking in many cells. Sections stained by the hematoxylin-eosin method show that most of the cells are distinctly acidophil, and that cells deeply stained with hematoxylin are exceptional. Sections fixed in bichromate solutions show brownish granules in the cytoplasm. A few contain large, round, hyaline bodies, occasionally containing dark, rodlike structures.

The nuclei (fig. 2) show some characteristic features. In the first place, they vary in size as much as do the cells themselves: occasionally a nucleus is not more than from 5 to 8 microns in diameter; most frequently it is from 15 to 30 microns long and, not rarely, much larger, depending on the size of the cell. Its location is most frequently eccentric, and in many cells its flattened appearance along a cytoplasmic edge gives the cell a striking resemblance to the "signet ring" cell of a Krukenberg tumor. A syncytial arrangement is not at all rare. One notices also that, occasionally, the nucleus is so pyknotic as to resemble a mere nuclear fragment. The shape of the nucleus is highly irregular: most frequently it is oval or cylindric, irregularly round or flattened out; occasionally it is almost triangular; not infrequently it is so highly bizarre as to be indescribable architecturally. Many cells are multinuclear, and from time to time one sees a cell in which the nucleus is very large and resembles a ball of twisted worsted. The staining of the nucleus is also irregular, but in an overwhelming majority of the cells the nucleus is always distinctly hyperchromatic. Even here, however, the staining is never uniform, the different parts of the nucleus staining with varying intensity. The chromatin network is usually coarse and in many cells irregularly twisted. In some cells the nucleus

is vesicular and has a "washed-out" appearance. This is particularly frequent in multinucleated cells. In most cells, the nucleus contains several nucleoli and, at times, very dark, irregularly shaped granules. The presence of fat or glycogen has not been established. In malignant tumors, mitotic figures are frequent, as are chromatin-rich nuclei (embryonic cells?). To sum up the appearances of the cells and of their nuclei, we should say that the most striking feature is the irregularity of size, shape and staining properties. Peyron regarded the

Fig. 2.—High power magnification of the tumor tissue, showing the variation in size, shape and position of the nuclei; reduced from × 340.

formation of irregular cellular masses through invasion of the fibrous septums as an early sign of malignancy.

It has been mentioned that these tumors are rich in capillaries. These are, as pointed out by Alezais and Peyron, separated from the tumor tissue by vascular endothelium. Of the vascular spaces there are two types: those in contact with the external surfaces of the epithelial cords and containing erythrocytes and largely neutrophil leukocytes, and the intra-epithelial capillaries, the meshes of which are perpendicular to the capillaries of the first type and contain cloudy, grumous material.

CHEMISTRY OF PHEOCHROMOCYTOMA

Qualitative demonstrations of the presence of epinephrine in the tumor were done in several cases, but the quantitative determination was carried out only by Rabin, who found the amount of epinephrine much larger than the normal. Since there is no method of demonstrating hyperadrenalemia, its relation to hypertension remains unsettled.

REPORT OF A CASE

This is the second case in the article by Lazarus and Eisenberg. The case was only mentioned in that article. Because of its many unusual features, such as its malignancy, its association with another primary malignant neoplasm of the thyroid gland, unusual places of metastasis—e. g., the gum, etc.—the complete description and the discussion of the case have been reserved for this article, dealing as it does with a complete study of all pheochromocytomas reported in the world's literature.

Clinical History.—A Russian Jewess, aged 63, was admitted to Sydenham Hospital on Jan. 1, 1930, complaining of a painful mass on each side of the neck and a small growth on the left lower gum. The latter growth had reached the size of a large pea three weeks after the extraction of the left lower bicuspid. Ten years before examination, she had noticed a slight swelling in the right submaxillary space. About four years before examination, she had noticed that her neck was getting larger; one year before examination, this swelling had caused her neck to become quite large. She refused surgical relief. About three months before examination, she began experiencing fairly constant backache and transient headache, and during the last three months had lost 25 pounds (11.3 Kg.) in weight, as well as noticed nodular masses on each side of her neck. A reference has already been made to the extraction of a tooth, promptly followed by the appearance on the gum of a reddish growth, the size of a large pea.

Physical examination revealed a sallow woman about 60 years of age, cachectic-looking and greatly depressed. The growth in the gum was tender and friable and bled easily. The thyroid gland felt hard and was irregularly and considerably enlarged. Bilateral inguinal as well as cervical adenopathy was present. Percussion sounds varied from dulness to flatness over the bases of the lungs and the left upper lobe, and there were coarse râles and tubular breathing over these areas. Examination showed nothing else that was significant, except pain over the dorsal and lumbar vertebrae.

Roentgenologic examination revealed metastatic nodules in both lungs.

All the laboratory data were negative, except the results of examinations of the blood, which were, so far as we have been able to ascertain, unique in cases of pheochromocytoma. The patient came into the hospital with a total white cell count of 22,000 and the following differential count: segmented neutrophils, 60 per cent; nonsegmented neutrophils, 10 per cent; monocytes, 5 per cent; lymphocytes, 6 per cent; basophils, 1 per cent, and eosinophils, 18 per cent. She also had moderate secondary anemia. Gradually the total count rose to 63,000, with the nonsegmented (band) neutrophils constituting 50 per cent; the lymphopenia persisted, and the eosinophilia persisted during the entire course, ranging between 10 and 25 per cent.

Another important feature was the absence of hypertension, the blood pressure ranging between 130 systolic and 85 diastolic and 120 systolic and 75 diastolic.

The patient's progress was steadily downward, and on Feb. 27, 1930, she died.

Résumé of Postmortem Examination.—The left side of the mouth was filled with a fungating, necrotic mass. Several large, discrete, firm lymph nodes were felt on each side of the neck.

The thyroid gland was not recognizable as such, there being in its place a piece of homogeneous, soft tissue, the size of a tangerine, encapsulated, but with the capsule perforated and invaded in several places. On section, the tissue was grayish yellow and contained numerous hemorrhagic and necrotic spots.

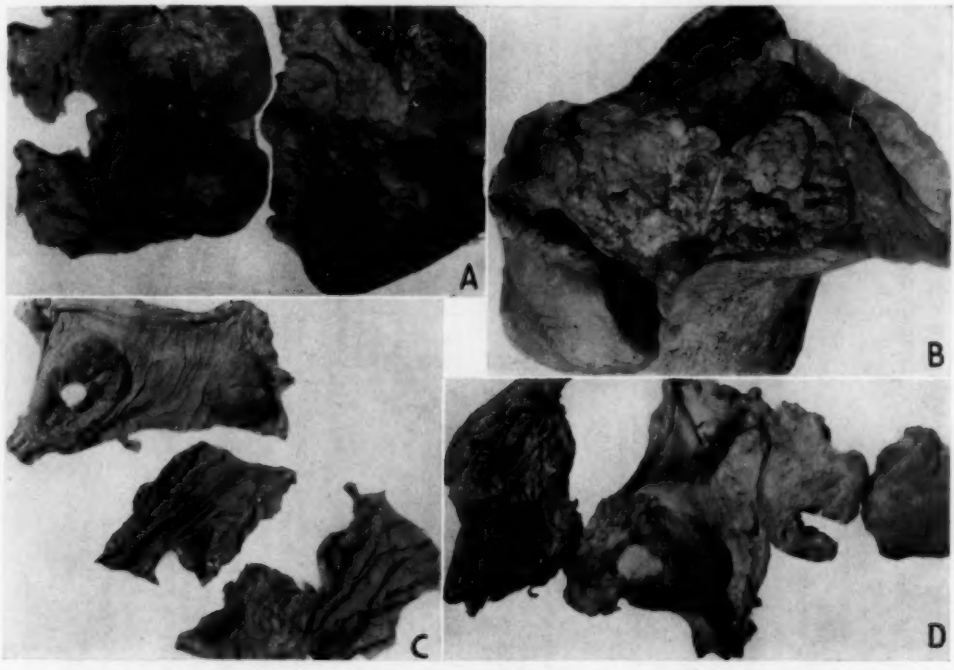

Fig. 3.—Pheochromocytoma: *A*, primary growth in the suprarenal glands, with kidneys normal; *B*, metastasis to the lung; *C*, metastasis to the intestines; *D*, metastasis to the mesenteric glands.

When the chest was opened, a necrotic mass was found in the upper lobe of the left lung, the size of an orange, adherent anteriorly to the five upper ribs, and a smaller mass in the lower lobe, anteriorly. The right lung showed an entire lobe converted into a similar necrotic mass (fig. 3*B*).

The liver, normal in size, contained a few superficial metastatic foci.

The spleen, fully twice as large as the normal, showed the lower half converted into homogeneous, grayish, necrotic tissue.

Both kidneys were normal.

Both suprarenal glands were destroyed and replaced by two masses of soft, grayish, necrotic tissue, each with just a thin rim of the cortex. These masses were twice the size of the normal glands (fig. 3*A*).

Cases of Pheochromocytoma Collected from the Literature

Author	Patient Sex	Patient Age	Symptoms	Gross Appearances	Histologic Appearances
Barker	M	47	Weakness, dyspnea, hypertension, epileptiform attacks, for 6 months	Cystic, broken-down tumor of left suprarenal medulla; generalized arteriosclerotic lesions in brain; hemorrhage in peduncles, pons and fourth ventricle; no metastases	Immature chromaffin cell tumor
Berdez	M	70	Died of pneumonia	Brownish-red tumor, 3 by 2 cm.	Cellular tumor; groups of cells separated by capillary nets, some of which are large enough to occupy one half the visual field; cells resemble medullary cells
Bergstrand	F	40	Hypertension	Tumor of right suprarenal	Paraganglioma
Bieble and Wichels	M	36	Hypertension, diabetes, sclerotic kidneys, traumatic loss of eye (war), dizziness, pseudobulbar paralysis, sudden unconsciousness and death	Bilateral suprarenal tumors; left, size of hen's egg; right, plum size; tumors dark grayish-red; basal vessels sclerotic; foci of apoplectic softening in basal ganglions; frank pontile bleeding; no metastases	Chromaffin cell tumor
Bonnamour, Doubrow and Montegue	?	?	Malignant paraganglioma with metastases to lymph nodes and pleura; in the latter, the growth differed from that in the former in that it contained no blood vessels and the cells were much less differentiated		
Connor	M M F	40 to 50	Benign tumors associated with hypertension		
Fränkel	F	18	Scarlatina at 14; hypertension, vomiting and headaches	Bilateral suprarenal tumor; right, size of nut; left, size of fist; both give chromaffin reaction	Called angiosarcoma, but probably paraganglioma
Gravier and Bernheim	?	?	Blood pressure 105/50	Bilateral malignant tumor with metastases to mediastinum	
Harbitz	M	47		Hypernephroma of left kidney with metastases; cystadenoma of pancreas; right kidney shows metastases from left, and a tumor of suprarenal	Paraganglioma
Hedinger	F	34	Died a few days after abortion; general clinical symptoms not clear	Left suprarenal has mass (10 cm.), encapsulated, adherent to diaphragm and pancreas; largely cystic, with shreddy tissue in the wall; no metastases	Cystic paraganglioma (struma medullaris cystica suprarenalis); positive chromaffin reaction
Helly	M	43	Hypertension, glycosuria	Tumor of right suprarenal, size of apple	Paraganglioma
Herde	F	62	Glycosuria, arteriosclerosis	Tumor of right suprarenal, 7 by 6 by 5 cm.; few small, reddish-gray cysts	Paraganglioma
	F	45	Hypertension	Bilateral suprarenal tumor; left, 3 cm. in cross-section, grayish-red; right, 1 cm., with few cystic areas; cardiac hypertrophy	Bilateral paraganglioma; frequent giant cells; much glycogen in left tumor
Herxheimer	M	55	Neurofibromatosis	Tumor of right suprarenal	Paraganglioma
Kawashima	F	33	Adnexal disease; macerated fetus; no hypertension; neurofibromatosis of skin	Tumor of left suprarenal	Primary hyperplasia of medullary cells, apparently paraganglioma

Kerppola	?	?	Hypertension	Tumor of suprarenal medulla	Paraganglioma
King	M	30	Loss of weight for 12 months; pain in joints; operated on for goiter 4 years previously; several subcutaneous nodules on chest and abdomen	Bilateral suprarenal tumor; left, 5 by 2 cm.; right, smaller; metastases to liver, lungs, bones, brain; chromaffin reaction positive	Malignant paraganglioma
Labbé, Azerad and Violle	M	29	Hypertensive crises (pallor, anguish, tachycardia, etc.)	Chronic glomerulonephritis; right suprarenal weighs 120 Gm.	Paraganglioma
Labbé, Tinel and Doumer	F	28	Diabetes; vomiting attacks 3 to 4 times a week; paroxysmal hypertension, 260/180 to 150/100	Kidneys normal; tumor of left suprarenal	Paraganglioma
Laignel-Lavastine and Aubertin	M	35	Chronic tuberculosis, melanoderma	Whitish nodule, size of pea, in right suprarenal	Medullary adenoma
Lascagna	M	61	Unable to work; cough for eight months	Bilateral suprarenal tumor, each gland weighing 55 Gm.; left tumor 9 by 6 by 2.5 cm.; right, 9 by 4.5 by 3 cm.	Paraganglioma (?), general structure showing giant cells, mosaic appearance, richness of capillaries; positive chromaffin reaction; no metastases
Lazarus and Eisenberg	F	58	Hematuria, pyuria and pain in left lumbar region; progressive loss in strength	Ovoid tumor of left suprarenal, 12.5 by 8.5 by 6 cm., cystic, filled with clotted blood and pseudomucinous material, rimmed with cortex	Pheochromocytoma
	F	62	Progressive enlargement of thyroid; nodule on left lower gum following extraction of tooth; loss of weight and strength; mass in right renal region	Bilateral suprarenal tumor; metastases to liver, lungs, bones, intestines, glands and gum	Malignant pheochromocytoma
Manasse	F	Old	Died from pulmonary tuberculosis	Tumor of left suprarenal, size of hen's egg	Paraganglioma
	M	64	No information	Tumor of left suprarenal, size of hen's egg	Paraganglioma
Marchetti	M	15	Bilateral tumor (10 and 11 Gm.), apparently paraganglioma and ganglioneuroma, as he says his case resembles that of Bruchanow, Dagonet, etc.		
Masson	?	?			Paraganglioma
	?	?		Metastases to lymph nodes and liver	Malignant paraganglioma
Masson and Martin	F	45	Cachexia; pain in right side of abdomen for few months; died 6 hours after operation	No autopsy; only small piece of tissue available	Malignant paraganglioma (?)
Mayo	F	30	Hypertension, headache, vomiting	Tumor of left suprarenal medulla	Paraganglioma
Neusser and Wiesel	?	?	Marked arteriosclerosis		Chromaffin cell tumor
	?	?	Vasomotor instability; died 2 hours after extraction of tooth	Bilateral suprarenal tumor, cystic	Chromaffin cell tumor
Oberling and Jung	F	28	Pregnancy; blood pressure 250/190; after delivery, patient turned pale, with pulse 150, and died in 6 hours	Tumor of right suprarenal, size and shape of kidney	Paraganglioma
Orth	M	47	Hypertension, renal disease	Tumor of right suprarenal, size of duck's egg	Paraganglioma
Perley	M	70		Tumor of left suprarenal	Paraganglioma
Rabin	F	45	Chronic nephritis, hypertension, exophthalmic goiter	Tumor of right suprarenal, 4 cm.	Pheochromocytoma

Cases of Pheochromocytoma Collected from the Literature—Continued

Author	Patient Sex	Patient Age	Symptoms	Gross Appearances	Histologic Appearances
Riemer	F	46	Addisonian syndrome	Tumor of right suprarenal, cystic	Paraganglioma
Robert	M	46	Hypertension; right lumbar tumor	Mass involving right suprarenal and kidney, weighing 700 Gm.	Paraganglioma
Russum and Barry	M	56	Neurofibromatosis; large mass in right upper quadrant of abdomen	Neurofibromatosis of skin, urinary bladder and mediastinum; right "polymorphous cell perithelial sarcoma, probably derived from a neurofibroma"; left paraganglioma; multiple metastases from first tumor	Paraganglioma
Schroeder	F	42	Hypertension, diabetes	Arteriosclerosis; cardiac hypertrophy; atrophy of pancreas; bilateral suprarenal medullary tumor; right, size of small apple; left, size of fist	Paraganglioma
Shipley	F	26	Hypertension	Tumor of medulla of right suprarenal, 9 by 7 by 3.5 cm., with small cysts and hemorrhagic areas	Paraganglioma
Suzuki	F	60	Neurofibromatosis, pulmonary tuberculosis	Pulmonary, intestinal, left suprarenal and pelvic peritoneal tuberculosis; medulla of right suprarenal replaced by grayish-yellow nodule	Paraganglioma
	F	82	Pneumonia on right side, emphysema, chronic bronchitis	Arteriosclerosis; tuberculosis of lungs and lymph nodes, etc.; tumor of right suprarenal	Paraganglioma and lipoma; partial chromaffin reaction
	M	62	Sepsis, fractured femur, bronchopneumonia on right side	Tumor of left suprarenal, 10 cm., necrotic and cystic	Paraganglioma
Thomas	F	80	Irrelevant	Tumor of left suprarenal, 4.5 by 2 by 4 cm., cystic, reddish-gray; no metastases	Paraganglioma
Vaquez, Donzelot and Géraudel	M	37	Transient hypertensive attacks with pain (from lower extremities to the head—no vomiting, no convulsions)	Tumor of right suprarenal, 7 by 6.5 cm.	Paraganglioma
Wahl	F	2½		Malignant tumor with metastases	Neuroblastoma, ganglioneuroma and paraganglioma
Weber	F	40	Hypertension	Cystic mass; no histologic examination	Paraganglioma (?)
Wegelin	F	39	Pulmonary tuberculosis	Chronic tuberculosis of lungs, intestines and mesenteric glands; sclerotic kidneys; tumor of right suprarenal, 5 cm., soft, grayish-red	Paraganglioma
Wichels and Biebl	M	33	Hypertension; contracted kidneys	Tumor of right suprarenal, size of hen's egg	Paraganglioma
Zeckwer	F	36	Paralysis of right arm and leg 3 months prior to admission; positive Wassermann reaction; attacks of unconsciousness	Softening of right internal capsule; aortic syphilis, grayish-red tumor of medulla of left suprarenal, 4 by 3 by 2.5 cm.; neurofibromatosis of spinal nerves; no metastases	Chromaffin cell tumor; no metastases; no invasion of structures outside of suprarenal

The small intestine (fig. 3*C*) showed in several places, scattered throughout the jejunum and the ileum, nodular, pale, necrotic masses varying in size from that of a pea to that of a cherry. In several places these growths, located in the intestinal mucosa, had perforated and had caused adhesions between adjacent loops. Several mesenteric glands (fig. 3*D*), ranging in size from that of a cherry to that of a tangerine, were found. The left psoas muscle showed, in its middle third, a soft, necrotic growth, the size of a plum. The five upper ribs in the axillary line on the left side were converted, for a distance of 8 cm., into soft, necrotic tissue, as were the bodies of the sixth, seventh, eighth, ninth and tenth dorsal vertebrae.

Examination revealed nothing else that was significant, except moderate myocardial fibrosis and atherosclerosis.

Microscopic Examination.—The tumor of the thyroid gland was a papillary adenocarcinoma. No metastatic growths from this could be discovered. All other neoplastic tissues described in the separate organs were alike, none of them showing any resemblance to the carcinoma of the thyroid gland.

Sections from these tissues, taken from the suprarenal glands, the lungs, the bones, the small intestine, the mesenteric nodes, the spleen and the liver, and a biopsy specimen of gum showed the following uniform picture: a very cellular growth, very richly vascular, with abundant thin connective tissue septums, giving the tumor a trabecular, alveolar appearance. Numerous capillaries lay in close contact with the cellular cords.

The striking feature was the extreme irregularity in the size and the shape of both the cells and the nuclei, as well as in the location of the latter in relation to the cytoplasm. The cells showed finely granular cytoplasm, and in sections fixed in bichromate solution numerous brown granules were seen—the chromaffin reaction. The cells varied in size tremendously, being from 15 to over 75 microns long, were most frequently polyhedral or ovoid, and were acidophil. Here and there were monstrously large cells resembling histiocytes. Homogeneous, hyaline bodies were observed in some cells.

The nuclei also varied greatly, some being pyknotic and hyperchromatic, others vesicular and pale, containing one or more nucleoli and, occasionally, black, rod-like granules. Their location was, for the most part, eccentric, a few cells showing the nucleus flattened out at one edge, the cells then resembling the "signet ring" cells of a Krukenberg tumor. A syncytial arrangement was frequent.

No glycogen or fat could be demonstrated by special staining methods.

Pathologic Diagnosis.—Bilateral malignant pheochromocytoma of the suprarenal gland, with metastases to the mouth (gum), lungs, liver, spleen, left psoas muscle, mesenteric glands, small intestine (with multiple perforations), sixth to tenth dorsal vertebrae and five upper left ribs; papillary adenocarcinoma of the thyroid gland, without metastases; fibrous myocarditis, and moderate diffuse atherosclerosis.

Summary.—A Russian Jewess, aged 63, with a history of enlargement of the neck in the region of the thyroid gland over a period of ten years, showed, on admission to the hospital, large lymph nodes on both sides of the neck and a small growth on the left gum. She had lost 25 pounds (11.3 Kg.) in weight during the previous three weeks. Roentgenologically there were metastatic nodules in both lungs. She had a high leukocyte count (60,000), which gradually came down to normal, and persistent eosinophilia (from 10 to 25 per cent). The blood pressure was normal at all times. She died three weeks after her admission to the hospital. The autopsy revealed, in addition to moderate generalized atherosclerosis and fibrous myocarditis, a papillary adenocarcinoma of the thyroid gland without

metastases, and a malignant bilateral suprarenal pheochromocytoma with metastases to numerous viscera and bones. Death was undoubtedly due to multiple necroses and exhaustion.

REVIEW OF CASES REPORTED IN THE LITERATURE

The reader is referred to the accompanying table containing the names of the authors who have reported cases, and age and sex of the patient and the main clinical and pathologic features in each case.

SUMMARY

Fifty-three cases of pheochromocytoma of the medulla of the suprarenal gland collected from the literature are tabulated with their main clinical and pathologic features.

A new case of malignant pheochromocytoma of the medulla of the suprarenal gland is presented, with the following unusual features: (*a*) coexistence of another primary malignant neoplasm (of the thyroid gland), (*b*) widely spread metastases from the pheochromocytoma, with none from the carcinoma of the thyroid gland, and (*c*) a very unusual blood picture.

Only five of the fifty-three cases previously reported were malignant, all with widespread metastases.

Association of benign pheochromocytoma with other tumors is not rare, several cases having been reported of its association with multiple neurofibromas, with adenomas (of the thyroid gland, liver and pancreas) and with hypernephroma.

In only one case was a malignant pheochromocytoma associated with another primary malignant tumor.

All known cases of malignant suprarenal pheochromocytoma were bilateral.

The incidence of the tumor is about even as to sex; it is greatest on the right side and in patients in the fifth decade of life.

The most striking histologic features are: the greatest imaginable irregularity in the size and shape of the cells and of the nuclei, the chromaffin reaction and the rich vasculature.

The most interesting feature is the relation of these tumors to hypertension. About one half of all the patients showed hypertension, some with atherosclerosis and others without it. While in some cases of tumor of the suprarenal cortex hypertension was continuous, in a large majority of the cases of tumors of the suprarenal medulla in which it was present it was of paroxysmal type—but only in the cases in which the tumor was benign, as all patients with malignant medullary tumor showed either no hypertension at all or hypotension.

The attempts to correlate hyperplasia of chromaffin tissue with hypertension are not successful because of the absence of proof that

hyperadrenalemia exists in such cases, and also because it is not at all established that hyperadrenalemia is responsible for hypertension.

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JAMES BRYCE AND HIS TEST FOR PERFECT VACCINATION

A FORGOTTEN CHAPTER IN THE HISTORY OF IMMUNOLOGY

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I

Long before the modern study of allergy, modified forms of smallpox ("varioloid") and of vaccinia ("vaccinoid") were explained by the previous action on the body of the variolous or vaccinial virus. In the modern phrase, these modified forms, as well as certain related phenomena, were interpreted as manifestations of specific sensitization. The earliest description of the allergic relationship between smallpox and vaccinia is given by Jenner in a footnote to case 4 in his "Inquiry": [1]

Case IV. Mary Barge, of Woodford, in this parish was inoculated with variolous matter in the year 1791. An efflorence of a palish red colour soon appeared about the parts where the matter was inserted, and spread itself rather extensively, but died away in a few days without producing any variolous symptoms. She has since been repeatedly employed as a nurse to Small-pox patients, without experiencing any ill consequences. This woman had the Cow Pox when she lived in the service of a Farmer in this parish thirty-one years before.

The footnote reads as follows:

It is remarkable that variolous matter, when the system is disposed to reject it, should excite inflammation on the part to which it is applied more speedily than when it produces the Small Pox. Indeed it becomes almost a criterion by which we can determine whether the infection will be received or not. It seems as if a change, which endures through life, had been produced in the action, or disposition to action, in the vessels of the skin; and it is remarkable too, that whether this change has been effected by the Small Pox, or the Cow Pox, that the disposition to sudden cuticular inflammation is the same on the application of variolous matter.

Instances more or less like the one described by Jenner in Mary Barge are described in the same year by George Pearson in his book about cowpox:

A man, 26 years, had cowpox six years previously, inoculated with smallpox. On the fifth day the appearance was like that of a gnat bite and it was thought that the inflammation seemed to be too rapid for that of variolous infection when it produces the smallpox.

In another case inoculation with smallpox virus of a young man who had cowpox ten years previously resulted in inflammation that was judged to be premature with respect to smallpox. . . .[2a]

From the John McCormick Institute for Infectious Diseases.

1. Jenner, Edward: An Inquiry into the Causes and Effects of the Variolae Vaccinae, a Disease Discovered in Some of the Western Counties of England, Particularly Gloucester, and Known by the Name of the Cow Pox, London, S. Low, 1798.

2. Pearson, George: An Inquiry Concerning the History of the Cowpox, Principally with a View to Supersede and Extinguish the Smallpox, London, J. Johnson, 1798, (*a*) p. 15; (*b*) p. 34.

A servant girl had the cowpox early in life and years later she was inoculated, "but nothing took place, except the appearance of a red blush round the incision. . . ." [2b]

Jenner's remarkable statement, a pioneer record of an allergic phenomenon, apparently escaped the notice of writers and observers for more than one hundred years—a telling example of the truth in Benjamin Ward Richardson's remark about Jenner's "Inquiry": "No book so small, has been talked of so much; no book has been read from the original so little; no book of such dimensions has made the name of any author so famous." Von Pirquet,[3] for instance, made his elaborate study of vaccinial allergy without knowledge of Jenner's and later descriptions of the phenomenon or of the work in Jenner's time and subsequently on its practical value. For no sooner had Jenner described vaccination against smallpox than efforts began to find a test for the perfect vaccination. In most cases vaccination gave rise to a local lesion without marked constitutional symptoms. It was feared that it might act locally without inducing the desired general action. How was one to be assured that so mild a process would protect against smallpox? To use Jenner's conclusive test, namely inoculation of the vaccinated with smallpox matter, was impractical and dangerous.

John Pearson writes: [4]

. . . since Vaccine produced but little disorder of the constitution, and is not attended by an eruption on any part of the body, except that to which the infectious fluid is applied, it would be very desirable to have some criterion by which we could be assured that the vaccinated person has undergone that inexplicable change which secures him against the Small Pox.

Before long the allergic reaction of the skin to vaccine virus was used as such a criterion. The idea appears to have arisen in the minds of several vaccinators at the same time. Was perhaps Jenner's footnote the common source even if it is not mentioned? The leader in this now forgotten search for a simple test for perfect vaccination was James Bryce of Edinburgh.

In 1801, the *Annals of Medicine* printed this note:

Mr. Bryce, one of the Surgeons who inoculate the cow-pock at the Public Dispensary of Edinburgh, has been for some time engaged in making experiments, with a view to ascertaining some important particular in the history of that disease, the results of which he will communicate to the public.[5]

The outcome of these experiments was published in a book in 1802, four years after Jenner's "Inquiry." A second, enlarged edition was published in 1809 (figs. 1 and 2).

3. von Pirquet, C.: Wien. klin. Wchnschr. **19**:885 and 1407, 1906; Klinische Studien über Vakzination und vakzinale Allergie, Leipzig, F. Deuticke, 1907; Arch. Int. Med. **7**:259, 1911.

4. Pearson, John: General Observations on the Cow-Pox, in Willan, Robert: Vaccine Inoculation, London, R. Phillips, 1806, appendix, p. IX.

5. Ann. Med. **6**:486, 1801.

In this book, which is quoted frequently in the writings on vaccination, especially during the next forty or fifty years, Bryce discusses the general history of cowpox, the "advantages to society from the general practice of inoculation for cowpox," the "circumstances to be

PRACTICAL OBSERVATIONS

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INOCULATION

OF

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POINTING OUT A TEST OF A CONSTITUTIONAL AFFECTION IN THOSE CASES IN WHICH THE LOCAL INFLAMMATION IS SLIGHT, AND IN WHICH NO FEVER IS PERCEPTIBLE.

ILLUSTRATED BY CASES AND PLATES.

BY JAMES BRYCE,

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Edinburgh:

PRINTED FOR WILLIAM CREECH; AND T. CADELL, JUN. & W. DAVIES, LONDON.

1802.

Fig. 1.—Title-page of book by James Bryce on inoculation of cowpox, published in 1802.

carefully attended by those conducting the inoculation of cowpox," and the medical treatment of cowpox. I am concerned here especially with his "test of a constitutional affection in those cases in which the local inflammation is slight, and in which no fever is perceptible" or, as he has it on the title-page of the second edition, "a certain test of perfect vaccination."

In the course of his study of cowpox inoculation, he recollected

. . . some experiments which had been made with regard to the inoculation of smallpox. It was found, that if the same person was inoculated every day until the fever induced by the first inoculation supervened, all the other punctures

PRACTICAL OBSERVATIONS

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THE SECOND EDITION.

WITH AN

APPENDIX,

CONTAINING ADDITIONAL OBSERVATIONS, TOGETHER WITH A PLAN FOR EXTINGUISHING THE CONTAGION OF THE SMALLPOX IN THE BRITISH EMPIRE, AND FOR RENDERING THE VACCINE INOCULATION GENERAL AND EFFECTUAL.

BY JAMES BRYCE, F.R.S. EDIN.

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Alex. Smellie, Printer.

1809.

Fig. 2.—Title-page of second edition of James Bryce's book published in 1809.

quickly advanced in their progress; and that, in the course of a day from the time the fever or general affection began, even that puncture which had been last made, perhaps only twenty-four hours before, equalled in maturity the one first made, perhaps eight or nine days before, and from which the fever had arisen.[6a]

6. Bryce, James: Practical Observations on the Inoculation of Cowpox, ed. 1, Edinburgh, W. Creech, 1802, (*a*) p. 173; (*b*) p. 175; (*c*) p. 189; (*d*) p. 214.

Here Bryce probably had in mind the experiments of Woodville, who wrote:[7]

> Thus if a person be alternately inoculated with variolous matter, and with that of the Cow-pox every day till the fever is excited, all the inoculations make a progress; and as soon as the whole system becomes disordered, they appear to be all equally advanced in maturation.

Bryce reaches the significant conclusion that because the pustule caused by the last puncture suddenly reached maturity at the time of the general or constitutional affection, "this alone was a sufficient proof of the presence of the variolous action in the system." He reasons that the same sort of reaction would occur in cowpox or vaccinia. The events in probably accidental inoculation in the course of vaccination supported him in this view:

> And certainly, if we find in cowpox, where the inflamed and hard areola does not take place, at least in the regular course of that affection, until the end of the seventh or beginning of the eighth day from inoculation, that a second inoculation, performed for example at the end of the fifth or beginning of the sixth day, is so much accelerated in its progress, about the time the general affection of the system usually takes place, as to have an areola formed within a few hours, or very shortly after the first, and that this areola increases with the first, and again fades at nearly the same time, we must be struck with the similarity and be forcibly led to draw the same conclusion in this case as in the former, respecting the smallpox, viz., that although the inoculated affection had appeared very slight, and no fever had been observed, yet that a certain action had been excited in the constitution. That this was the true constitutional affection of cowpox, may be judged by the acceleration of the second vesicle to a state of maturity, five days before this could have happened had there been no consentaneous general action or change in the system.[6b]

Two children who had been vaccinated successfully by Bryce some months before were inoculated with the virus of smallpox. In both "the variolous inoculation advanced regularly" and well formed pustules developed, in one case by the sixth day and in the other by the eighth, when they quickly dried up without "the smallest general indisposition." Here Bryce describes a clearcut example of the reaction of sensitization or partial immunity to the smallpox virus noted by Jenner and others.

Here it may be noted that in 1802 Coxe[7a] described accelerated and abortive reactions from vaccination and from variolation "when the system is disposed to reject" the infection (see his page 23). He gives a letter (page 70) from Benjamin Waterhouse, dated March 28, 1802, in which are described the attempts to vaccinate seven persons who had

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7. Woodville, William: Reports of a Series of Inoculations for the Variolae Vaccinae, or Cow-Pox, with Remarks and Observations on This Disease, Considered as a Substitute for the Small-Pox, London, R. Phillips, 1799.

7a. Coxe, John Redman: Practical Observations on Vaccination: Or Inoculation for the Cow-pock, Philadelphia, James Humphreys, 1802.

gone through smallpox. "By the fourth day I was able to pronounce, that six of them would not have the genuine Vaccine pustule. They inflamed too quick; the inoculated part resembled the sting of a bee, and wanted the requisite hardness, as well as that deep-seated, well-defined, and slowly-progressing affection, which characterises the genuine incipient pustule." In thirteen or fourteen days scarcely any mark of the reactions was left. Waterhouse, who had been inoculated with smallpox in 1774, also describes an accelerated process from the insertion of vaccine matter in the hollow between the thumb and the finger of his left hand.

Having studied in detail several cases of second vaccination some days after the first, Bryce concludes

> . . . that if, during the regular progress of cowpox, a second inoculation be performed a certain number of days after the first, the affection produced by this second inoculation will be accelerated in its progress so as to arrive at maturity, and again fade at nearly the same time as the affection arising from the first inoculation; and that this will take place although the constitutional affection be so slight as otherwise to pass unnoticed.[6c] . . . It is, therefore, to be wished that this test may soon be generally practised as an improvement of much importance in conducting the inoculation of cowpox, as at once giving confidence in the extent of the ailment, and precluding any necessity for any future inoculations with the virus of smallpox.[6d]

Briefly stated, Bryce's test was made by inoculating the other arm from the primary vesicle on the fifth day after the first inoculation. If the constitution was affected, that is, if the body was responding to the specific antigenic action of the vaccine first inserted, the vesicles on both arms would arrive at maturity together and also fade together.

II

It is interesting to follow the reception of Bryce's proposal as reflected in the literature of the period. The test and the principle on which it is based are discussed by Bell,[8] Adams,[9] Willan,[10] Moore,[11] Monro [12] and others; I have not attempted to track down all the refer-

8. Bell, George: A Treatise on the Cow-Pox, Containing an Enumeration of the Principal Facts in the History of That Disease, the Method of Communicating the Infection by Inoculation and the Means of Distinguishing Between the Genuine and Spurious Cow-Pox, Edinburgh, W. Laing, 1802.

9. Adams, Joseph: A Popular View of Vaccine Inoculation, etc., London, R. Phillips, 1807, p. 41.

10. Willan, Robert: Vaccine Inoculation, London, R. Phillips, 1806.

11. Moore, James: The History and Practice of Vaccination, London, J. Callow, 1817.

12. Monro, Alexander (tertius): Observations on the Different Kinds of Small Pox and Especially on That Which Sometimes Follows Vaccination, Illustrated by a Number of Cases, Edinburgh, A. Constable & Co., 1818, p. 281.

ences to the matter. But first I must introduce the observations of Henry Hicks by way of an excerpt from Baron's "Life of Jenner." [13]

I have already mentioned Henry Hicks as his [Jenner's] friend and counsellor: I have also mentioned how sedulously he promoted vaccination by first submitting his own children to it, and then diffusing it in his neighbourhood; I have now to attempt to commemorate his services in another line. He made himself perfectly acquainted with all the details of cowpox inoculation; and about this time he brought this knowledge into practice. He commenced a series of inoculations; and evinced an accuracy and fidelity which would have done honour to the most enlightened physician. To show that this is no exaggerated praise I will mention that in a letter to Dr. Jenner, dated the second of August, 1799, he communicated an observation which at a subsequent period was also noticed by Mr. Bryce, of Edinburgh, and which led that gentleman to propose the only thing like an improvement in the practice of vaccination that was not suggested by Dr. Jenner himself. In two of the persons whom Mr. Hicks had vaccinated he found that "the arms came on so slowly that on the sixth day the pustules were not more forward than they generally are on the third or fourth: added to which, there appeared so much irregularity in them that I thought it better to show their arms to Mr. Darke." Two days afterwards Mr. Hicks determined to re-vaccinate them. The result he communicated in the following words: "The second inoculation seemed to make immense strides to overtake the first; and, what is wonderful, the first pustules began to change their character and put on the true vaccine appearance." He also made another remark which proves how quickly he detected every peculiarity in the progress of the affection. He adds, "I must not forget to tell you that Chamberlain's child, before the inoculation, had some eruptions on its arm and back, and as the vaccine pustule came on, these pustules assumed the exact vaccine character, and became perfect cowpox pustules." It is due to Mr. Hicks to declare that there is more original and satisfactory information to be derived from his remarks than from those of all the individuals who had written on the subject, from the time of the publication of Dr. Jenner's Inquiry.

Shortly after Bryce's book appeared, George Bell [8] addressed a book on cowpox to the clergy of Scotland, "who deservedly have great influence over the minds of people, and are much disposed to promote every proposal that tends to the public good." Bell discusses the work of both Woodville and Bryce. He does not approve fully of Bryce's double inoculation although he accepts the typical result as "a pretty certain test of the virus having entered the constitution." He recommends inoculation with smallpox when it is desirable to subject the patient who has passed through cowpox to the most certain test, and he describes in detail the appearance of the smallpox puncture "when the constitution is armed against the infection, by having previously passed through the vaccine disease." Three varieties of reactions are described, which obviously had been observed in the course of inoculation by Bell himself:

1. In the first of these, a few hours after the variolous matter is inserted, the puncture inflames, and continues nearly in the same state for eight, nine, or ten

13. Baron, John: The Life of Edward Jenner, London, H. Colburn, 1838.

days, the redness never varying much, or extending over a greater space than about the eighth part of an inch in diameter.

2. In the second, the puncture inflames soon after the variolous matter is inserted, and very early produces a pustule containing matter, which pustule recedes suddenly about the sixth or seventh day; and in this case may be reckoned a certain test of the patient having been previously affected with Cow-pox.

3. The last and most important variety, is that in which the pustule is inflamed on the day after inoculation, and continues to increase regularly till the tenth or eleventh day, when it is at its height, and when from the soreness of the part the patient becomes sick, and is sometimes affected with startings similar to those that precede convulsions. In this case, the inflammation is commonly of the size of a half-crown piece, but is of a darker colour than in Small-pox, and has not so much erysipelatous redness as the Cow-pox. The pustule is of a livid colour; on being punctured, it rarely gives out any matter; and where it contains a fluid, this does not readily produce any marked disease on being used in inoculation.

The inflammation begins to recede about the eleventh day; and on the fourteenth or fifteenth, is scarcely perceptible, leaving, in the place of the pustule, a brownish scab, similar to that which remains where the inoculated Small-pox has failed.

This variety, which is not uncommon, is more like the genuine Small-pox than any of the others; but it differs essentially from Small-pox in the following circumstances. It is never accompanied with any eruption in other parts of the body; the pustule does not follow the same regular progress with that of the Small-pox; and matter taken from it does not so readily propagate the Small-pox, as the virus does which is taken from a patient who is labouring under the ordinary form of the disease.

It appears, therefore, in all cases of doubt, to be a safe precaution, either to repeat the vaccine inoculation, or to inoculate the patient for the Small-pox.

Early in 1805, T. Hugo published a letter,[14] which I give in full:

About the sixth day, when the Vesicle on the inoculated part is formed, or about three days before the areola may be expected to come on, I insert the point of a lancet into the Vesicle, and with the lymph which exudes, I inoculate the other arm. The progress of the second Inoculation is very dissimilar to that of the first. The Vesicle proceeds more rapidly through its stages, exhibiting an areola at the same time as the Vesicle on the other arm, and being, on the ninth or tenth day, in an equal state of forwardness, but more diminutive. I consider this as so decisive a test of constitutional affection, especially in children, that unless it takes place, I never venture to warrant my patient's security against Variolous affection, but advise that the inoculation should be repeated at a subsequent period. Having acted in this cautious manner for several years, and having always taken the Virus at the earliest possible period, I have had the most satisfactory proofs of its efficacy, in resisting the contagion of the Small-pox.

In 1805, John Pearson[4] writes as follows:

In the early part of the year 1801, I ascertained, that if a second inoculation with vaccine fluid be performed on the sixth or seventh day after the first, a pustule will arise, which proceeds in the usual manner, until the efflorescence appears round the pustule produced by the first inoculation; and that, as soon as

14. Hugo, T.: M. & Phys. J. **13**:48, 1805.

this takes place, the second pustule begins to fade, and two or three days afterwards, disappears altogether. On mentioning this as a test of the specific action of vaccine fluid on the constitution, it was suggested, that a proposal of this kind might diminish the confidence of the public in the new inoculation. I acquiesced in the objection, and did not attempt to introduce this new mode of practice.

Commenting on this statement, in 1817, James Moore [11] remarks:

The forbearance of Mr. Pearson at that critical period was much approved of by Dr. Jenner. . . . It is singular, that in the same year—Mr. Bryce, a respectable surgeon at Edinburgh, also made experiments similar to those made by Mr. Pearson. Each were unquestionably independent of the other; and Mr. Bryce published his in the year 1803 [1802], conceding that they would convey useful information.

This gentleman, indeed, tried the effect of revaccination during every period of the progress of a vaccine vesicle. He noticed that, when the first operation succeeded the inflammation excited by the second was accelerated; and, as soon as the primary vesicle acquired the areola, the second, however small it might be, also acquired a proportional areola, and both desiccated together.

Mr. Bryce, like Mr. Pearson, observed that this peculiarity of the second vesicle proceeded from the influence of the first; and he concluded that it might be relied upon as a sure test of the constitution being properly influenced, and secured from the Small-pox in future.

Robert Willan [10] in 1806 repeats that Bryce's test is founded on experiments by inoculators of smallpox, presumably Woodville in particular, which showed

. . . that if the same person was inoculated every day until the fever induced by the first inoculation supervened, all the other punctures quickly advanced in their progress, and that in the course of a day from the time the fever or general affection began, even that puncture which had been last made, perhaps only twenty-four hours before, equalled in maturity the one first made, perhaps eight or nine days before, and from which the fever had arisen.

Joseph Adams [9] first refers to Woodville's observation that if two inoculations of smallpox are made at an interval of three or four days, "both the inoculated places will arrive at their height at the same time." He then says: "The same has also been observed of cow-pox, and this is now so well known that the second insertion has been proposed as a test of perfect vaccination." Finally he offers the following observation as proof of the identity of the morbid poisons of smallpox and cowpox:

For if small pox is inserted to-day, and the same subject inoculated three or four days after with cow pox, or with cow pox today, and three or four days after with small pox, the same consequences will follow as if both insertions had been of small pox only, or of cow pox only; that is, each will arrive at maturity at the same time, and the only difference will be that the last insertion will produce a smaller pustule or vesicle.

Here again is a prototype of the test for antigenic immune relationship of the present day.

In 1818, Alexander Monro III writes that Bryce's test was so much approved of by Dr. Jenner that after having spent much pains in preparing a plan of his own, Jenner laid it aside after Mr. Bryce's plan was published and had the candor to state his perfect approbation of every part of it, and his utmost reliance on its efficacy in rendering the smallpox extinct.[12] Monro also writes:

> My Father, in his Lectures, used always to express his utmost confidence in Mr. Bryce's test as a mark that the constitution has been affected, and also his opinion that its ingenious author merited a public reward; as without this improvement, he considered Dr. Jenner's discovery to be incomplete.

In reply to the objection that Bryce's test unduly complicated the process of vaccination, Monro urges, as now is the rule, that the patient should be seen more than once in order to determine whether the vaccination runs its regular course, and states that the neglect of this precaution is responsible for many of the failures.

What did Jenner think of Bryce's test for perfect vaccination? The answer in part, at least, is in the letters on the subject in Baron's "Life."[13]

> About this time [1802] Dr. Jenner received from Mr. Bryce of Edinburgh, a copy of that gentleman's treatise on cow-pox, accompanied with a very polite letter, in which he very modestly says, that he had added only "some new hints" on the subject.
>
> Mr. Bryce to Dr. Jenner.
>
> Sir,
>
> I presume to address you on the present occasion because I think it may be pleasant for you to learn that your favourite subject the inoculation of cow-pox, for which society must ever be indebted to you, has not been altogether neglected in this corner of the world.
>
> Convinced as I am of the power of the cow-pox in shielding the human constitution from the attacks of small-pox, and being placed some time ago in a situation favourable for making observations on that interesting subject, I did not fail in marking down whatever occurrences appeared to me worthy of notice, and these I have now presumed to publish.
>
> I have taken the liberty of desiring Messrs. Cadell and Davies, booksellers, to forward you a copy of this my publication.
>
> You will no doubt, Sir, find a great deal of your own labours scattered throughout this essay; for your investigations on the subject have been so full and so satisfactory that it is impossible to say much on the subject without interfering with you. I trust, however, you will also find some new hints, which your ingenuity may improve farther than I have yet been able to do.
>
> It would afford me much pleasure, Sir, if you will favour me with your sentiments on the two most prominent features of my publication; namely, the new mode proposed for obtaining and preserving the virus of cow-pox, and the proposed test of a constitutional affection. Should any objections occur to you on these points, which I have not foreseen, I trust that you will have the goodness to mention them freely; for this appears to me to be the only way by which we can arrive at truth in our investigations.

It affords me much pleasure, Sir, to observe that you are likely to reap some fruits from your labours. And while a grateful nation bestows a worldly remuneration to her benefactor, it shall be my care to . . . (the remainder of this letter is wanting).

Of the "two most prominent features," as Mr. Bryce in his essay terms them, the opinion of Dr. Jenner will be best learned from a perusal of extracts from his replies to Mr. Bryce's communications.

Dr. Jenner to Mr. Bryce, Edinburgh.

Dear Sir,

Before I enter on the subject of your present letter allow me to return you my most sincere thanks for your former one, and for your valuable publication on the cow-pox. Although you have found me so tardy in my acknowledgments, yet be assured the very handsome manner in which you mention my name in that work has not passed away without exciting in me a grateful remembrance of your own. You have anticipated some few observations that I had noted down for my next number.

You may easily conceive how incessantly I am toiling if you consider the immense extent of the correspondence that must necessarily fall upon me; and let this consideration make some allowance for my apparent neglect of your letter. I can with trust assure you that I have made efforts to answer it, fifty times since it has been in my possession.

Again, he writes thus to Mr. Bryce—April 5, 1803.

It afforded me great pleasure to find that the Vaccine virus I sent you put an end to all your solicitudes respecting the perfection of that you had been previously using, and that you have diffused it so widely through the towns and villages of Scotland.

I doubt not that you will with much ease establish an institution for inoculation, on a plan equally useful with ours in London. I should send our plan, but it is not yet in print.

I much admire your precaution in using a test of the certainty of infection; and your ingenuity in the manner in which you employ it. To all young vaccinators it cannot be too strongly enjoined. The experienced will determine from the character of the pustule. The evidence before the House of Commons evinces the propriety of your observations.

I put your crust into the hands of my friend Ring, and he informed me yesterday that it had produced a good pustule. Experience now tells us that this is a good mode of sending the Vaccine virus to distant parts.

Bryce was perhaps the first to use the crust, or scab, as the source of vaccine virus. Early American writers on vaccination comment on the value of the method to them.

Bryce also describes [15] an immediate local redness about the point of vaccination, observed frequently in children with a skin of delicate texture, the appearances exactly resembling the inflamed spot around the sting of a bee. He regards this reaction as indicating "certain success from the operation."

15. Bryce, James: Practical Observations on the Inoculation of Cowpox, Pointing Out a New Mode of Obtaining and Preserving the Infection, and Also a Certain Test of Perfect Vaccination, ed. 2, Edinburgh, W. Creech, 1809, p. 130.

In the early French [16] and Italian (Sacco [17]) experiments to determine how soon vaccination protects against smallpox, the peculiarities of the variolous eruption on inoculation soon after vaccination are described clearly. And Sacco, "the Italian Jenner," independently observed the accelerated development of the vesicles of revaccination a few days after primary vaccination. He ascribes this course to a gradual loss in disposition of the vaccinated person. I can do no better than to quote his own words in his "Trattato di vaccinazione": [17a]

> In order to withdraw cowpox material for some time from one person, I inoculated various persons from one arm to the other, and I observed always that the last inoculation produced new pustules, which were more rapid in their course and caught up with the first pustules in the incrustation. I explain this as follows: The pustules develop in accord with the disposition of the vaccinated for smallpox, depending on the strength or weakness of which they develop more or less. Consequently the first pustules, which strike the disposition wholly uninjured, develop in full force and regularity; the disposition however can not be consumed completely at once and thus the second inoculation two or three days later will produce an effect according to the character of the remaining disposition and develop more rapidly and more irregularly. If one would inoculate again after six to seven days, it would be of no use because the disposition is then completely absent and neither a vaccine nor a smallpox pustule will appear.
>
> The Englishman Crighton in his decision of the genuineness or spuriousness of vaccine appears to have had a similar theory in mind as he recommends to inoculate the vaccinated again after six to seven days. In case the pustules of the second inoculation by rapid and irregular course caught up with the first, then he regarded the first as regular and active; but on the other hand if the second pustules passed through a regular and undisturbed course, then the first inoculation was false and inactive. But this interpretation of vaccination would be applicable only when by some accident all the pustules were scratched off and one would be in doubt as to the preceding eruption. Otherwise the genuine cowpox is accompanied with such definite and unmistakable signs that no doubt is possible and the method consequently is superfluous and useless.

I have not succeeded in obtaining any definite inkling of the identity of the Englishman Crighton (Crichton?) to whom Sacco refers. No such name occurs in the English writings that I have read on the subject in question. Sacco's work was translated into German by Wilhelm Sprengel,[17b] who adds this footnote to the passage in which Sacco mentions Crighton:

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16. Rapport du Comité central de vaccine, Paris, 1803, p. 257. Bousquet, J. B.: Nouveau traité de la vaccine et des éruptions varioleuses, Paris, J. B. Baillière, 1848.

17. Sacco, Luigi: (*a*) Trattato di vaccinazione con osservazioni sul giavardo e vajuolo pecorino, Milan, tipog. Mussi, 1809, p. 49; (*b*) Ludwig Saccos Generaldirektors der Vaccination im Königreiche Italien und ersten Arztes am grossen Krankenhause zu Mailand, neue Entdeckungen über die Kuhpocken, die Mauke und die Schaafpocken (translated from the Italian by Wilhelm Sprengel), Leipzig, 1812.

Bryar [Bryce] in Edinburgh recommends to inoculate with the lymph of the first pustule 36 hours before the development of the redness about the pustule. This would be on the fifth or sixth day after the first inoculation. If now at the time the whole body is affected the progress of the second inoculation has been so accelerated that redness appears and disappears with the red zone of the first inoculation, then the inoculation has acted fully. (Edinburgh Med. and Surg. J., 1805, V. II, p. 250.) Spr

This note shows that Bryce's test was known in Germany at that time.

In 1840, Robert Ceely [18] described the reaction to variolous inoculation followed by vaccination in the cow in this wise: "Here was Bryce's test on the cow: Variola on one side in Vigour, tested by vaccine on the other, hastening to declare the fact of a constitutional affection."

Bryce's work did not pass unnoticed in this country. Far from it. Coxe [19] in Philadelphia used his method with success. Samuel Scofield,[20] the first resident surgeon to the New-York Institution of the Inoculation of the Cowpock, established in 1802, describes Bryce's test in detail in his book, "Vaccina or Cowpock," published in 1810. Three methods have been proposed, he says, for testing the constitutional effect of vaccination: [20a]

. . . the first, by Jenner, consisted in variolous inoculation soon after the person had passed through vaccina; this is a direct and clear test, but dangerous. The second method, Dr. Pearson, is a second inoculation of vaccine matter; objectionable because of practical difficulty. The third, and best, is a second inoculation during the progress of the first as proposed by Bryce.

Scofield also says "that Bryce appears to be the first who recommended the use of the scab as a substitute for the virus." Before leaving the institution named, Scofield, at the request of the medical board, tested a number of persons from among the first to have been vaccinated "by introducing the fluid matter of smallpox into both arms of each of them. On the third day from the inoculation the patients were examined, and, with one or two exceptions, the virus appeared to have taken effect; by the sixth day, however, the inflammation surrounding the punctures had entirely subsided, and not the least symptom of fever or eruption ever occurred in either of them." [20b] Here is described once more the specific reaction of allergy to the virus of smallpox.

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18. Ceely, Robert: Observations on the Variolae Vaccinae, as They Occasionally Appear in the Vale of Aylesbury, with an Account of Some Recent Experiments in the Vaccination, Retro-Vaccination and Variolation of Cows, Tr. Provincial M. & S. A., 1840; printed in Crookshank, E. M.: History and Pathology of Vaccination, London, H. K. Lewis, 1889, vol. 2.

19. Coxe, John Redman: Observations on Vaccination, M. Repository **1**:114, 1804.

20. Scofield, Samuel: A Practical Treatise on Vaccina or Cowpock, New York, Collins & Perkins, 1810; (*a*) p. 102; (*b*) p. 25.

Stephen Brown,[21] in his prize essay, refers to Bryce's experiments in detail, but doubts whether the test will become general on account of the additional labor and the objection of mothers. John Eberle [22] also refers to Bryce's test for the "sufficiency of recent vaccination," but adds that smallpox inoculation is the most certain test.

Among later writers to discuss Bryce's test, I mention especially Thomas Watson and George Gregory, whose descriptions and comments, written about 1850, merit citation. First, Gregory: [23]

> Another variety of anomalous, or what is called modified cow pox, presents itself when the vaccine virus is reinserted on the fourth, fifth, or sixth day from the primary vaccination. The result is, that the vesicles of the secondary vaccination form rapidly, and are hurried forward in their course, so as to overtake the first crop, when the whole maturate and scab together. The secondary vesicles are thus necessarily much smaller than the primary. Mr. Bryce, in 1802, ingeniously proposed to avail himself of this law, with the view of ascertaining whether the system was under the full influence of vaccination. The plan, though it never received the sanction of Dr. Jenner [this statement is open to doubt], has nevertheless enjoyed great popularity, and is everywhere known by the name of Bryce's test. He recommends that the second application of the virus should take place on the evening of the fifth or morning of the sixth day, so that the new vesicles may have from thirty-six to forty-eight hours to grow, before constitutional or irritative fever is set up. Of late years, this procedure has fallen comparatively into disuse. In cases where the primary vaccination proves unsatisfactory, it is now more usual to recommend a repetition of the operation at the interval of one, two, or three years, according to the extent of the apparent imperfection. I believe this to be a great improvement on the plan of Mr. Bryce.
>
> When re-vaccination is practised at distant periods from the primary insertion of the virus, the arm very generally presents the appearances of modified cow-pox—that is, the vesicles advance with abnormal rapidity. Areola forms around them on the fourth or fifth day. The resulting scabs are small, and fall off in a few days.

Thomas Watson [24] writes as follows:

> Of course it is of much moment to determine whether the cow-pox has run its proper course or not; and it is not always easy to say how far the progress of the cow-pox may deviate from that which has just been described, without failing of its protective influence. A very ingenious test of this, free from all ambiguity, has been devised by Mr. Bryce. His plan is this. He vaccinates the other arm, or some other part of the body, four or five days after the first vaccination. If the constitution has been properly affected by the first operation, the inflammation of the second vesicle will proceed so much more rapidly than usual, that it will be at its height, and will decline and disappear, as early as that of the

21. Brown, Stephen: Am. M Recorder **16**:45, 1829.

22. Eberle, John: A Treatise on the Practice of Medicine, ed. 2, Philadelphia, J. Grigg, 1831.

23. Gregory, George: Lectures on the Eruptive Fevers, Am. ed. 1 (edited by H. D. Bulkley), New York, S. S. and W. Wood, 1851, p. 253.

24. Watson, Thomas: Lectures on the Principle and Practice of Physic, Philadelphia, Lea & Blanchard, 1844, p. 870; 1853, p. 1157.

first: only the vesicle and its areola will be smaller. In fact, from the time of the formation of the areola, the second vesicle is an exact miniature of the first. If the system has not been duly influenced by the first vesicle, the second will run its own course, increasing up to the eighth day, and so on. Should this be the case, the second vesicle should be tested by a third.

We find the germ of this criterion in the early history of vaccination. Dr. Jenner vaccinated the children of his friend Mr. Hicks, the first gentleman who consented to adopt the practice. This Mr. Hicks became afterwards an expert vaccinator himself, and it was his custom in a doubtful case, to perform a second vaccination a few days after the first; and he remarked that the second vesicle made "immense strides to overtake the first."

Bryce's test did not survive in practice. As early as 1820 John Thomson [25] wrote to Bryce that "the test proposed by yourself is not generally had recourse to in this country" (Scotland). But the interest of medical writers in the significance of the changes in the reaction to vaccine and variolous virus continues to manifest itself on to the end of the century. It appears clearly, however, that the classic writings on this topic by Jenner, Bryce and others were not studied carefully. The observations and reflections of Trousseau [26] merit special mention. In his lectures on clinical medicine, he describes the following experiment apropos of secondary autovaccination by children:

I vaccinate: in four days I make a new puncture with a lancet charged from one of the incipient pustules; I continue to do this daily; and you have seen that up to the ninth and sometimes till the tenth day—but not later than that—there is a cow-pock developed at each new puncture. The secondary pocks, however, do not attain to the size of the primary pock, . . .

When he speaks of modified vaccinia, one is reminded of Sacco's explanation,[17] for Trousseau says:

. . . when the economy is in no state of aptitude for receiving or developing the virus of small-pox or cow-pox, the puncture made in vaccinating produces no more effect than if the lancet had been charged with pus from a common boil; when there is some partial aptitude, the result is abortive cow-pox at the end of some days; when there is a state of still greater aptitude, the pock, quicker in its evolution than in the normal order of events, closely resembles that of regular cow-pox; but it passes away more rapidly.

This statement anticipates clearly the interpretations today of the allergic reactions to vaccine virus as applied to problems of practical vaccination.[27] Trousseau's statements are reechoed in all the seven edi-

25. Thomson, John: An Account of the Varioloid Epidemic, Which Has Lately Prevailed in Edinburgh and Other Parts of Scotland, London, Longman, 1820; also Philadelphia, H. C. Carey, 1824.

26. Trousseau, A.: Lectures on Clinical Medicine Delivered at the Hôtel-Dieu, Paris (translated by John Rose Cormack), Philadelphia, Lindsay & Blakiston, 1869.

27. Leake, J. P., and Force, J. N.: Pub. Health Rep. **45**:2793, 1930.

tions of Flint's "Treatise on the Principles and Practice of Medicine" [28] published from 1863 to 1886, in this form:

During the progress of the vaccine affection vesicles having the distinctive characters of vaccinia have sometimes been observed on other parts of the body. It is probable that these are caused by the patient scratching the vesicles on the arm and carrying therefrom lymph containing the virus on the finger-nails to parts where, owing to the abrasions of the skin, self-vaccination is the result. Experiments show that between the fourth and the ninth or tenth day the characteristic vesicles may be multiplied at will by revaccinating with lymph from the vesicles produced by the primary vaccination. . . . Incomplete vaccinia—vaccinoid, as it was termed by Trousseau—is denoted by the vesicles being developed more quickly and progressing to desiccation more rapidly, by their swollen size and conoidal form, and by the absence of cicatrices or of the appearance distinctive of the true vaccine cicatrix.

In 1883, and again in 1890, Joseph Jones [29] in New Orleans reprinted Jenner's "Inquiry" and other early writings on vaccination, including the description from Monro of Bryce's test and Jenner's letter to Bryce, dated April 5, 1803. Jones states that in 1817 the Cow-pox Institution in Dublin reported favorably on Bryce's test, and he comments on the "simple and beautiful" demonstration of the constitutional effects of vaccination afforded by the distinctive reactions of early revaccination.

Brouardel's statement in 1898 [30] about the development of immunity after vaccination is remarkably lucid and comprehensive:

We have now to consider how long a time elapses after vaccination before immunity against smallpox is acquired, and how long this acquired immunity lasts. Jenner proved the reality of the immunization by submitting young James Phipps to the test of smallpox inoculation two months after having been vaccinated; it was found that he was refractory to the variolous poison. But how soon after vaccination does this immunity appear? Bryce, the Bousquet vaccine commission, Vetter, and Trousseau have determined this very exactly. They made fresh inoculations every day after the primary vaccination, and found that immunization was definite by the tenth day. Up to that time pustules developed at the seat of the puncture, but these later lesions, said Trousseau, did not reach the size of the first, those being less typical which were the result of the later vaccinations. Thus those of the ninth and tenth days aborted soon after showing a slight degree of inflammation, while after the tenth day there was no specific reaction.

Ten days after vaccination, therefore, the subject has acquired immunity to vaccina, but we have yet to see how the case stands in regard to smallpox immunity.

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28. Flint, Austin: A Treatise on the Principles and Practice of Medicine; Designed for the Use of Practitioners and Students of Medicine, ed. 6, Philadelphia, Lea Brothers & Co., 1886.

29. Jones, Joseph: Contagious and Infectious Diseases, Measures for Their Prevention and Arrest, Baton Rouge, L. Jastremski, 1883. Medical and Surgical Memoirs; Containing Investigations on the Geographical Distribution, Causes, Nature, Relations, and Treatment of Various Diseases, 1855-1890, New Orleans, 1876-1890, vol. 3, pt. 1.

30. Brouardel, P.: Vaccinia, Twentieth Cent. Pract. **8**:501, 1898.

Sacco (Trattato di Vaccinazione, Milan, 1809) and the committee [French] on vaccina employed the same means to determine this as were employed to determine vaccinal immunity. They inoculated children with smallpox on each day following vaccination. As long as the inoculations were not made later than the fourth day after vaccination, says Bousquet, the two eruptions developed simultaneously with the same ease and the same liberty as if each had occurred separately, preserving, however, the relations which ought necessarily to result from the difference of dates. The inoculated variola thus preserves its ordinary characters. But towards the fifth day, and especially after the sixth, while the variolous eruption occurs at the point of inoculation, there is no general eruption nor is there any febrile reaction. The inoculations made on the ninth or tenth day are followed by very poorly defined local lesions, and after the eleventh day the local symptoms fail to appear in the great majority of cases. Thus we see that smallpox immunity is acquired in almost the same time as is that against vaccinia.

Welch and Schamberg (1905) [31] give a clear account of Bryce's test, which they say has not been accorded much endorsement, and has fallen into disuse. Finally, it is of interest to note that the "American Illustrated Medical Dictionary" [32] defines Bryce's test as follows: "The determination of a degree of immunity against smallpox conferred by vaccination by repeating the inoculation after the lapse of several days: if the first is successful, the second will rapidly overtake it."

III

Who was James Bryce?

I have been unable to learn when he was born and when he died. The few facts I can give about him and his work have been learned mostly from his publications [33] which are listed in the "Index Catalogue of the Library of the Surgeon-General's Office, U. S. Army."

He was fellow of the Royal Society of Edinburgh; member of the Royal College of Surgeons and president in 1816 and 1817; surgeon to the Orphan Hospital, and one of the surgeons to the Institution for the Gratuitous Inoculation of Cow-Pox, also called the Vaccine Institution of Edinburgh, founded in 1801, where he carried on the work on his test for perfect vaccination.

So far as I have been able to find, his first publication deals with an account of yellow fever in 1792 on board the Burbridge East Indiaman, on which he was surgeon. It was his third voyage. The ship left Downs for Madras on April 15, 1792. May 26 the equator was crossed when yellow fever broke out. Of the three hundred patients all told

31. Welch, W. M., and Schamberg, J. F.: Acute Contagious Diseases, Philadelphia, Lea Bros. & Co., 1905.

32. Dorland, W. A. N.: The American Illustrated Medical Dictionary, ed. 16, Philadelphia, W. B. Saunders Company, 1932.

33. There is a brief and incomplete account of Bryce in: Biographisches Lexikon der hervorragenden Ärzte aller Zeiten und Völker, 1929, vol. 1, p. 742. Here his name is given as James B. Bryce.

under his care, only three died. There are two copies of this account in the Army Medical Library in Washington, and both contain the handwriting of the author (fig. 3).

In addition to his book on cowpox, he wrote about variolous inoculation after vaccination in 1811, and in 1818 appeared a letter from him in the *Edinburgh Medical and Surgical Journal* on the opinions of that day in regard to the antivariolous power of vaccination.

Notes and comments on his work and reviews of his books were published from time to time in the *Annals of Medicine* and the *Edinburgh Medical and Surgical Journal* until about 1813. He wrote also (1815) on the fetal liver, and attributed the large size of the liver in the fetus at birth to the blood it contains which at birth goes into the lungs.

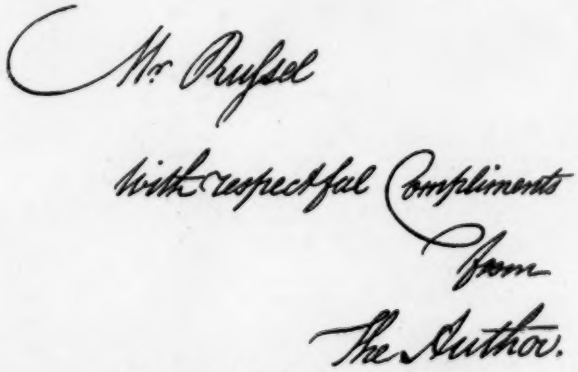

Fig. 3.—Handwriting of James Bryce.

In John Thomson's book [25] (Edinburgh, 1820) about a varioloid epidemic, "which has lately prevailed in Edinburgh and other parts of Scotland," are letters from Bryce in which he discusses with ability and insight the probable nature of the disease or diseases described by Thomson.

Bryce was an inventor and pioneer advocate of the stomach pump. August 4, 1824, he showed the Medico-Chirurgical Society a siphon for emptying and washing out the stomach, particularly in cases of laudanum and other forms of narcotic poisoning. At that time, and also earlier, he lived in St. Andrews Square in Edinburgh. The value of Bryce's instrument was reported promptly by Allison,[34] who used it with success in a case of laudanum poisoning in a man, 35 years old.

The quotations I have given from his writings show that Bryce was a keen and thoughtful observer. He recognized clearly the significance

34. Allison, P. W.: History of a Case Confirming the Efficacy of the Means of Evacuating the Stomach, in Cases of Poisoning, Proposed by Mr. Bryce, Edinburgh M. & S. J. **23**:416, 1824.

of the reactions on revaccination and on variolous inoculation of vaccinated persons. Whether he may be credited with absolute originality in his interpretation is of course doubtful. He himself speaks of the clue afforded him by the experiments of others with successive variolous inoculations. And it seems almost certain that he had read carefully Jenner's "Inquiry," although he makes no mention of Jenner's footnote on the change produced by smallpox or cowpox in the reactivity of the skin to variolous matter. Bryce did not hesitate to turn his observations into a practical test for perfect vaccination, hoping to increase the benefits of vaccination and to preclude the need for any further inoculations with the virus of smallpox. He promptly and properly submitted his proposed test for consideration and criticism by Jenner. Bryce thus had the power to carry into effect a measure that he believed would be of practical value.

In brief, the work by Bryce on "a certain test of perfect vaccination" is admirable. The theory was sound, the experiments adequate, the test itself simple and practical. And, devised in 1802, it has the distinction of being the first test for specific allergy.

* * * * * *

It was only natural that with the years the interest diminished in the peculiar reactions to smallpox and cowpox virus described so clearly and interpreted so soundly by Jenner, Bryce, Sacco and others. As smallpox yielded to vaccination, experimental human variolation ceased completely. Vaccination became a universal routine, carried out blindly, and the outcome was determined more and more "by the character of the pustule" as Jenner said would be the case. And so Bryce's test was forgotten and with it also the early records of the mysterious constitutional effects subsequently designated as allergy or sensitization. To this day all that splendid work remains neglected in the literature on immunity. The success and extent of vaccination were due in large measure to the ease with which the specific virus could be handled safely. The great principle of protective inoculation could not be applied effectively to diseases other than smallpox until Pasteur demonstrated how other viruses might be obtained in suitable forms. With the expansion of immunization, active and passive, came the discovery of serum disease and the rôle of sensitization in its manifestation and finally the complete and independent rediscovery of vaccinial allergy by von Pirquet.[3] If the pioneer work in that field had been known then, who would question its influence on allergic research in general or its stimulus to better understanding of the practical significance of the allergic reactions in revaccination?

THE REACTION TO FOREIGN MATERIAL IN THE NORMAL AND IN THE INFLAMED GALLBLADDER

AN EXPERIMENTAL STUDY

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An experimental attempt was made to determine if there exists in the wall of the normal or the inflamed gallbladder an organized group of cells or a system of histiocytes. The gallbladder is a complex histologic and cytologic structure consisting of five layers of tissue. It was considered possible that the histiocytes are arranged as a structural and functional unit of the cytologic structure of the gallbladder. The presence of an organized group of histiocytes similar to, if not identical with, the units of the reticulo-endothelial system (von Kupffer cell in the liver, reticulocytes in the spleen, and so forth) would be significant in interpreting certain cytologic, physiologic and pathologic observations.

Observations were made on dogs and rabbits. All operative procedures were made under ether anesthesia and with sterile technic. A complete necropsy was made on each animal. Sections from selected tissue were stained with hematoxylin and eosin, scarlet red, van Gieson's stain, eosin, alum-carmine or hemalum.

PARTIAL BLOCKAGE OF THE RETICULO-ENDOTHELIAL SYSTEM WITH TRYPAN BLUE

A fine suspension of carbon material was injected intravenously into rabbits. The daily amount varied from 2 to 20 cc., and the total quantity injected varied from 0.5 to 72.8 cc. for each kilogram of body weight. At necropsy, the liver, spleen, bone marrow, lymph nodes, lungs, medullae of the adrenal glands, and the kidneys were stained black. The degree of staining varied with the quantity of carbon material that had been injected. After 30 cc. or more of carbon material for each kilogram of body weight had been injected intravenously, carbon granules could be observed in the wall of the gallbladder. The majority of carbon granules were in the cytoplasm of polyblasts and macrophages in the immediate vicinity of the capillary vessels.

Trypan blue was injected intravenously or intraperitoneally in dogs and rabbits. The wall of the gallbladder was stained blue in each case, but it was difficult to distinguish clearly extracellular or intracellular trypan blue granules.

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INJECTION OF CARBON MATERIAL INTO THE LUMEN OF THE NORMAL GALLBLADDER

A suspension of carbon material was injected into the lumen of the gallbladder in dogs and rabbits. In no case were carbon granules observed in the wall of the gallbladder or in the regional lymph nodes.

INJECTION OF CARBON MATERIAL INTO THE WALL OF THE NORMAL GALLBLADDER

In several dogs, a fine suspension of carbon material was injected into the wall of the gallbladder. The animals were killed from four to eight days later. The carbon material was entirely phagocytosed by polyblasts and macrophages of local origin. Phagocytic cells were in every layer of the gallbladder, but were most numerous in the tunica fibrosa externa.

INJECTION OF VARIOUS TYPES OF FOREIGN MATERIAL INTO THE WALL OF THE INFLAMED GALLBLADDER

In several dogs, acute hemorrhagic cholecystitis was produced by the intravenous injection of Dakin's solution. Carbon material or cholesterol with emulsified fat was then injected into the wall of the gallbladder. The animals were killed from two to four days later. The carbon material and globules of fat were observed in the cytoplasm of numerous polyblasts and macrophages. Only a few particles of the injected material were extracellular. It appeared as if the inflammatory reaction produced increased phagocytic activity.

RESULTS

When vital dyes or suspensions of finely particulate material are injected intravenously, they are quickly removed from circulation. The cells responsible for this elimination are the units of the reticulo-endothelial system, which are principally situated in the sinusoids of the liver, spleen, bone marrow, lymph nodes and medulla of the adrenal gland. Small quantities of graphite injected intravenously into rabbits disappeared rapidly from the peripheral blood stream. At necropsy, the organs mentioned as containing special divisions of the reticulo-endothelial system were uniformly colored black. Particulate carbon was never demonstrated in the wall of the gallbladder of the rabbit following the intravenous injection of small quantities of graphite. Only after the more advantageously situated reticular cells, such as the phagocytic endothelial cells lining the sinuses or sinusoids of the liver and spleen, had been partially saturated, was any of the graphite deposited in the wall of the gallbladder. The quantity of particulate material necessary to produce this primary saturation varied somewhat with the state of the animal, but seemed to occur quite uniformly after the injection of 30 cc.

of graphite preparation for each kilogram of body weight. This condition may be compared to a physiologic threshold of the reticulo-endothelial system for particulate matter.

The first carbon particles that appeared in the wall of the gallbladder following intravenous injection were in the cytoplasm of the cells immediately surrounding the smaller capillaries. They increased in size and number as the total quantity of carbon injected into the animal was increased. At no time could endothelial cells be observed to detach themselves from the wall of the vessel, nor could they be found in the wall of the gallbladder as single carbon-containing units. This is in agreement with Lang's [1] observation on the endothelium of the capillaries in aseptic inflammation. Many peculiar cells were concentrically arranged about the peripheral portions of the endothelial cells. These cells, which have been designated as pericytes by Zimmermann,[2] were not only arranged about the arterioles, capillaries and the larger vessels, but appeared as detached individual cells, free in the tissues. In the transition from a fixed to a detached, mobile state, they changed from a thin, curved cell, with a central, oval nucleus, to a round or oval cell, similar in appearance to a small polyblast. In many sections, cells about the vessels displayed such remarkable resemblance to lymphocytes that a hematogenous origin had to be considered as a possibility. At no time, however, were any lymphocytes observed in migration from the lumina of the vessels to the tissue. Granular leukocytes were not found in the wall of the gallbladder. The entire process presented the appearance of a mild, localized, cellular reaction to an aseptic inflammation. It appears, therefore, from the data at hand, that most if not all of the phagocytic cells were derived from resting wandering cells, polyblasts, pericytes and histiocytes.

Particulate carbon produced intense irritation when injected directly into the wall of the gallbladder. The type and uniformity of the cellular response were remarkable. The cells that contained the particulate carbon were arranged in three superimposed, concentric layers. The first layer was in the submucosa, the second layer in the large connective tissue septums of the muscularis, and the third layer in the tunica fibrosa externa. These have been called the internal, middle and peripheral layers. The peripheral layer was the thickest. In these laminae the majority of cells were round, oval or polygonal, and their size varied from about 15 to 40 microns in diameter. In observing the structure of the graphite-containing cells it is essential to realize that the carbon is frequently crowded into every available portion of the cytoplasm.

The reaction to foreign material in the wall of the experimentally inflamed gallbladder consisted of a combination of the cell types observed

1. Lang, F. J.: Arch. Path. **1**:41, 1926.
2. Zimmermann, K. W.: Ztschr. f. Anat. u. Entwicklgsgesch. **68**:29, 1923.

when the two conditions were produced separately. When particulate carbon and cholesterol had been injected into the wall of the gallbladder, it was possible to distinguish granules of carbon material and globules of cholesterol in the cytoplasm of many histiocytes. The phagocytosis of fat by the histiocytes of the subcutaneous tissue of rabbits has been described by Kusnetzowsky [3] and Anitschkow.[4] The cells that phagocytose fat in the subcutaneous tissue of the rabbit are apparently morphologically similar to the histiocytes that phagocytose foreign material introduced into the wall of the gallbladder of the dog.

The histiocytes of the gallbladder of man may be instrumental, if not a decisive factor, in restricting many inflammatory processes. The gallbladder is exposed to infection from two surfaces. The mucosa is in direct contact with the contents of the lumen, which may and frequently does contain virile, pathogenic organisms. Cholecystitis is frequently restricted to the mucosa and submucosa. In pericholecystitis, however, the inflammatory changes are restricted to the outer layers. The active participation of the histiocytes of the gallbladder in the defense against bacterial invasion may be a larger factor in arresting or limiting injury.

SUMMARY

The reaction to foreign material in the wall of the normal and the inflamed gallbladder was observed. It was found that in the gallbladder of the dog and rabbit the histiocytes, owing to the distribution of the connective tissue, are arranged in three concentric layers. The majority of the histiocytes in the wall of the gallbladder, which under normal conditions are in an inactive stage, appear to develop from a preexisting local cell. The injection of particulate matter or vital dyes directly into the wall of the gallbladder of the dog produces rapid mobilization of the resting wandering cells into large, active, mobile, phagocytic histiocytes. These cells are identical with the histiocytes found in the connective tissue throughout the body. There is a possibility that a few histiocytes may develop from mononuclear, nongranular, hematogenous leukocytes, which have become lodged in the wall of the gallbladder. This must be considered as an accessory source. Histiocytes were demonstrated in the wall of the gallbladder of the rabbit by the use of vital stains. Carbon material was not absorbed from the lumen of the gallbladder of the dog or rabbit. In chemical cholecystitis, the inactive histiocytes are mobilized in large numbers. They rapidly phagocytose particulate matter, cholesterol and olive oil injected into the wall of the gallbladder. The arrangement of the histiocytes in three concentric layers suggests their function as a phagocytic cellular defensive mechanism in cholecystitis and other pathologic conditions of the gallbladder.

3. Kusnetzowsky, N.: Arch. f. mikr. Anat. **97**:32, 1923.
4. Anitschkow, N.: München. med. Wchnschr. **2**:2555, 1913.

PRODUCTION OF GASTRIC AND DUODENAL ULCERS IN EXPERIMENTAL CINCHOPHEN POISONING OF DOGS

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AND
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These experiments were begun in an effort to produce in dogs the acute degenerative changes in the liver alleged to occur occasionally in human patients who have taken cinchophen. The effect of cinchophen on the canine liver has been reported previously.[1] Postmortem examinations revealed that a large percentage of these animals had gastric and duodenal ulcers. This paper is a report of this phase of these experiments, which indicate that the feeding of cinchophen is the most effective means yet introduced for producing gastric and duodenal ulcers in dogs without operative procedures that disturb the normal anatomic relations of stomach and intestines.

PERTINENT FACTS FROM THE LITERATURE

Experimental work on the etiology of peptic ulcer began late in the nineteenth century with the work of Cohnheim. The abundant literature which has developed since that time has been so frequently reviewed that only the briefest reference to it is necessary in this paper. It is now known that the factors which may induce acute gastric erosions are not necessarily the same as those which produce the typical chronic indurated ulcers, although it seems probable that all chronic ulcers originate on the basis of acute erosions. Much confusion has arisen from the fact that many writers have failed to differentiate between factors tending to produce acute erosions and those tending to induce chronicity.

Etiologic Factors in Acute Erosions.—The numerous suggested factors in the causation of acute gastric erosions may be classified as circulatory, physical, chemical, bacteriologic and miscellaneous.

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Aided by a grant from the Committee on Scientific Research of the American Medical Association.

1. Churchill, T. P., and Van Wagoner, F. H.: Proc. Soc. Exper. Biol. & Med. **28**:581, 1931.

Virchow believed that infarction following embolism was the basis of the formation of gastric ulcers. Cohnheim [2] and others produced ulcers by injecting suspensions of metallic salts. Ivy [3] repeated this work, but failed to produce lesions when using an inert material. Von Bergmann [4] and Westphal [5] believed that arterial spasm was the cause of obstructed circulation.

The physical agents that have produced ulcers of the stomach are: x-rays (Wolfer [6]), heat (Decker [7] and Katzenstein [8]) and intense cold (Ribbert [9]). Excision of portions of the mucosa and of the mucosa and muscularis have been tried, but these defects heal with remarkable rapidity unless other factors are present, such as unabsorbed suture material.

The chemical agents may be subdivided into local escharotics and chemical and biologic poisons. Acute erosions have been produced by submucous injections of various chemicals, the most commonly used being silver nitrate. Superficial burns are sometimes associated with acute gastric erosions. This has been explained on a toxic basis. Gastrotoxic serums that cause ulcers have been produced experimentally. Ivy and Shapiro [10] produced gastric ulcers by means of local anaphylaxis.

Bacteria as possible factors in the production of ulcers have been advocated chiefly by Rosenow,[11] who reported the isolation of a specific strain of streptococci.

Berg and Jobling [12] believe that there may be a biliary or hepatic factor in the formation of some peptic ulcers. They observed gastric or duodenal ulcers in about 50 per cent of dogs with a Peyton-Rous permanent biliary fistula. Other etiologic factors that have been advocated are: a preexisting gastritis, embryonal rests in the gastric mucosa, vitamin deficiencies and endocrine disturbances.

Factors Inducing Chronic Changes in Acute Lesions.—Anatomic, mechanical and chemical factors are foremost in the formation of chronic peptic ulcer. Aschoff [13] believed that lesions along the lesser

2. Cohnheim, J.: Lectures on General Pathology, London, the New Sydenham Society, 1890, vol. 3, p. 875.
3. Ivy, A. C.: Arch. Int. Med. **25**:6, 1920.
4. von Bergmann, G.: Jahresk. f. ärztl. Fortbild. **12**:3, 1921.
5. Westphal, K.: Deutsches Arch. f. klin. Med. **114**:325, 1914.
6. Wolfer, J. A.: J. A. M. A. **87**:725, 1926.
7. Decker: Berl. klin. Wchnschr. **24**:369, 1887.
8. Katzenstein, M.: Berl. klin. Wchnschr. **45**:1749, 1908.
9. Ribbert, H.: Frankfurt. Ztschr. f. Path. **16**:343, 1915.
10. Ivy, A. C., and Shapiro, P. F.: Arch. Int. Med. **38**:237, 1926.
11. Rosenow, E. C.: J. A. M. A. **61**:1947, 1913.
12. Berg, B. N., and Jobling, J. W.: Arch. Surg. **20**:997, 1930.
13. Aschoff, Ludwig: Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924, p. 279.

curvature and prepyloric region of the stomach tend to become chronic because of the peculiar anatomic arrangement of this portion of the stomach, which he called the "Magenstrasse." In this region, the mucosa is arranged in taut longitudinal folds, and the blood vessels to this region are more indirect than elsewhere, and the circulation is interfered with by the muscular contractions of the stomach. The experimental work of Ivy,[14] Mann and Williamson[15] and McCann[16] lends support to the theory that mechanical factors play a part in the formation of chronic peptic ulcers. Surgical procedures have hitherto offered the best method of studying the effect of the acid gastric juice on the formation and healing of ulcers. Mann and Williamson[15] and others devised operations for shunting the alkaline content of the duodenum into some portion of the intestine other than the normal. By this method the gastric juice was thrown into an intestine deprived of the neutralizing secretions. These procedures produced acute and chronic ulcers in the intestine in a large percentage of the experiments. In addition to the factors named, there is indication that such factors as nutritional disturbances, toxemia and metabolic disturbances may play a part in the chronicity of ulcerative gastric lesions.

CINCHOPHEN

Cinchophen, or phenylquinoline carboxylic acid, was introduced into medicine in 1908 by Nicolaier and Dohrn. Since that time its use has increased in popularity until it is now employed extensively by physicians in the treatment of rheumatism, arthritis and gout. It is also widely used by the laity. In 1923, Worster-Drought[17] described the first case of toxic manifestations presumably due to cinchophen. Since that time eighty-one clinical cases of alleged cinchophen poisoning have been reported. In the cases in which autopsy was performed, the essential pathologic change consisted of acute yellow atrophy of the liver, and in only three of the few reports in which the gastro-intestinal tract is mentioned, are the gastro-intestinal lesions described: gastritis, petechiae of the intestinal mucosa and apthous ulcers of the mouth.

METHODS

Well nourished, apparently healthy dogs were used in the experiments. Each dog was given a daily dose of cinchophen, which had been thoroughly mixed with a meat and cereal preparation. They received the usual care accorded laboratory animals. In the majority of cases, the dogs were allowed to eat or not as they chose, and no forced feedings were employed. The rest of the dogs were fed in the same manner until food was persistently refused; then a varying number of

14. Ivy, A. C.: J. A. M. A. **75**:1540, 1920; **85**:877, 1925.
15. Mann, F. C., and Williamson, C. S.: Ann. Surg. **77**:409, 1922.
16. McCann, J. C.: Arch. Surg. **19**:600, 1929.
17. Worster-Drought, C. C.: Brit M J. **1**:148, 1923.

doses of cinchophen, suspended in cottonseed oil, were given by stomach tube. The daily dose of the drug administered was calculated on the basis of the average human therapeutic dose. If 150 pounds (68 Kg.) is considered as the average weight of the human body and 7.5 grains (0.49 Gm.) three times a day as the average dose, the human dose is approximately 0.33 grains (0.022 Gm.) per kilogram of body weight. The dogs were weighed at the beginning of the experiment, and the dose was calculated on the basis of this initial weight.

The dogs were closely observed as to symptoms, and postmortem examinations were made as soon after death as possible. A few, when their condition became extremely bad, were put to death under ether anesthesia. The stomachs were immediately removed, opened along the greater curvature and washed out. Some of the specimens were retained as gross specimens, but the majority were sectioned and stained by the routine hematoxylin and eosin method for microscopic examination. Portions of several of the ulcer-bearing stomachs were fixed in absolute alcohol and stained for mucin content by the mucicarmine method.

The lesions classified as acute ulcers were carefully differentiated from areas of postmortem digestion by microscopic demonstration of an inflammatory reaction in addition to the break in the mucosal continuity. Lesions were considered chronic only when deep penetration and reactive fibrosis could be demonstrated. Healing was determined by scar formation and contraction of the mucosa.

OBSERVATIONS

Number of Ulcers Produced.—The dogs were divided into four groups, depending on the daily dosage of cinchophen.

Group 1, consisting of five dogs, received twenty-seven times the normal human dose per kilogram (i. e., twenty-seven times 0.022 Gm. per kilogram). Two received 10 doses, and the rest 9, 8 and 3 doses, respectively. In the first three of these dogs ulcers developed.

Group 2 received ten times the normal dose per kilogram. The seven dogs in this group receiving 123, 24, 22, 20, 10, 8 and 8 doses, respectively. Ulcers developed in every dog.

Group 3 received five times the normal human dose per kilogram. There were five dogs in this group, receiving 118, 58, 21, 15 and 13 doses, respectively, and ulcers developed in all.

Group 4 received the normal human dose per kilogram. The seven dogs in this group received 101, 79, 71, 56, 6, 3 and less than 10 doses, respectively. Ulcers developed in the first four.

The results, as summarized in table 1, show that of the entire series of twenty-four dogs, nineteen, or approximately 80 per cent, acquired true gastric ulcers.

The total amount of cinchophen per kilogram of body weight necessary to produce gastric ulcers varied considerably. Thus, dog 20 showed ulcer formation after ingestion of only 1.23 Gm. of cinchophen per kilogram, while dog 15 was given 27.06 Gm. per kilogram. The average total amount ingested per kilogram was 5.06 Gm.

The minimum time required for the production of the ulcers cannot be stated with certainty, since there was no way of determining how

long the lesion had been present when autopsy was performed. However, dog 33 died from intercurrent infection eight days after the beginning of the experiment and showed acute ulcer formation. Likewise, dog 1 died from perforation of an ulcer after ingesting daily doses of the drug for a period of ten days.

Symptoms.—All of the dogs, except dog 1, early presented anorexia, which persisted throughout the course of the experiment. The majority of the dogs, in addition, showed occasional nausea and vomiting. Those which developed ulcers had tarry stools at intervals.

TABLE 1.—*Summary of Experimental Data*

Group	Dog	Initial Weight, Kg.	Total Amount Drug per Kg. Body Weight, Gm.	Total Dose, Gm.	Number of Doses	Length of Experiment, Days	Result
1	1	6.3	6.0	37.8	10	10	Ulcer
27 × N.H.D.*	2	7.8	6.0	46.8	10	20	Ulcer
0.6 Gm. per Kg.	4	7.8	5.4	42.1	9	15	Ulcer
	5	20.3	4.8	97.4	8	55	Negative
	6	23.5	1.8	42.3	3	20	Negative
2	15	6.1	27.06	165.1	123	156	Ulcer
10 × N.H.D.	19	11.2	5.74	64.3	24	51	Ulcer
0.22 Gm. per Kg.	34	8.3	4.84	40.2	22	25	Ulcer
	12	17.2	3.87	66.6	20	20	Ulcer
	25	8.6	2.00	17.3	30	30	Ulcer
	11	10.5	1.76	18.5	10	10	Ulcer
	33	8.3	1.76	14.6	8	8	Ulcer
3	22	16.2	12.95	209.8	118	143	Ulcer
5 × N.H.D.	18	11.9	6.56	77.8	58	79	Ulcer
0.11 Gm. per Kg.	24	8.7	2.36	20.5	21	47	Ulcer
	16	8.9	1.68	14.9	15	21	Ulcer
	23	12.4	1.42	17.5	13	26	Ulcer
4	17	13.6	2.26	30.6	101	121	Ulcer
N.H.D.	8	12.3	1.75	21.5	79	96	Ulcer
0.022 Gm. per Kg.	13	9.2	1.56	14.3	71	77	Ulcer
	20	12.5	1.23	15.4	56	113	Ulcer
	9	8.7	0.13	1.1	6	7	Negative
	21	16.2	0.06	1.0	3	6	Negative
	7	9.3	?	?	10	137	Negative
Average.....			5.06		(or less)		

Ulcers produced in 19 of 24 dogs, or 80 per cent

* N.H.D. = normal human dose.

There was a marked loss in weight in all the animals (table 2). This loss varied from 0.3 to 7.5 Kg., with an average loss in weight of approximately 3 Kg. Some of the animals lost as much as 44 per cent of their body weight during the course of the experiment, and—taking the group as a whole—there was an average weight loss of 23 per cent. This average loss per day was about 0.7 per cent.

Distribution of Ulcers.—The distribution of the ulcers was characteristic. In four of the dogs multiple gastric erosions were distributed widely throughout the mucosa. One dog showed only a single erosion, which was near the pylorus. There were thirty-four chronic gastric ulcers produced in these twenty-four dogs, and approximately 90 per

cent of them were located in the gastric pathway, including the entire pyloric canal, and about 70 per cent of the ulcers were found on the lesser curvature. The duodenal ulcers were all in the first portion of the duodenum, three being located on the anterior wall and one on the posterior wall.

Morbid Anatomy.—On pathologic examination, the lesions found in the stomach and duodenum were morphologically identical with the classic descriptions of gastric erosions and peptic ulcers. The following protocols indicate the types of lesions found.

Dog 1.—The peritoneal cavity was filled with a brownish, foul-smelling fluid, and the serous coverings showed marked hyperemia and were covered with fibrino-

TABLE 2.—*Summary of Effects of Cinchophen Poisoning on Weight of Animals*

Dog	Initial Weight, Kg.	Weight at Death, Kg.	Length of Experiment, Days	Weight Loss, Kg.	Weight Loss, per Cent	Weight Loss per Day, per Cent
1	6.3	6.0	10	0.3	4.7	0.47
2	7.8	6.4	20	1.4	17.9	0.90
4	7.8	6.6	15	1.2	15.4	1.03
5*	20.3	12.2	55	6.1	30.0	0.55
6*	14.1	11.3	20	2.8	20.0	1.00
7*	9.3	6.2	137	3.1	33.3	0.24
8	12.3	8.1	90	4.2	34.1	0.36
9*	8.7	8.0	7	0.7	8.1	1.16
11	10.5	9.2	10	0.7	6.7	0.66
12	17.2	11.5	20	5.7	33.1	1.65
13	9.2	5.7	77	3.5	38.0	0.49
15	6.1	4.1	156	2.0	32.8	0.21
16	8.9	7.1	21	1.8	20.2	0.96
17	13.6	9.5	121	4.2	30.6	0.25
18	11.9	7.8	79	4.1	34.4	0.44
19	11.2	8.2	51	3.0	26.8	0.53
20	12.5	7.0	113	5.5	44.0	0.39
21*	16.2	14.8	6	1.4	8.6	1.43
22	16.2	8.7	143	7.5	46.3	0.32
23	12.4	8.4	26	4.0	32.2	1.24
24	8.7	6.0	47	2.7	31.0	0.66
25	8.7	6.7	30	2.0	23.0	0.77
33	8.3	8.0	8	0.3	3.3	0.41
34	8.3	6.0	25	1.4	16.8	0.67
Averages.....				2.89	23.0	0.70

* Indicates dogs in which no ulcers developed.

purulent exudate. On the lesser curvature of the stomach, 1 cm. proximal to the pylorus, there was a small opening in the serosa, through which gastric contents could be expressed. When the stomach was opened, an ulcer was found opposite the perforation in the gastric wall. There was a moderate degree of hyperemia of the duodenum. This specimen was mounted, and no sections were made.

Dog 4.—The peritoneum was normal, except for a small, roughened, dull and lusterless area surrounded by a zone of hyperemia on the posterior wall of the stomach. When the stomach was opened, three ulcerated areas were found. These varied from 4 to 8 mm. in diameter. Two of these ulcerations were located in the pyloric canal, one on the lesser curvature and one on the posterior wall. The remaining ulcer was located on the anterior wall of the stomach just proximal to the isthmus. This ulcer microscopically showed destruction of the mucous membrane, the submucosa and portions of the muscular coat and was surrounded by an acute inflammatory reaction with very little fibrosis. The two pyloric ulcers showed deep penetration into the muscular coat. Microscopic section of one of

these ulcers showed absence of the mucosa, submucosa and a large part of the muscularis; its floor was covered with fibrin, which contained a few polymorphonuclear leukocytes; beneath this area were many polymorphonuclear leukocytes and red blood cells, and a large amount of fibrin. Still deeper was a zone of typical granulation tissue with a number of lymphocytes. Surrounding the ulcerated area there was a marked increase of fibrous tissue in the submucosa, muscular coat and serosa. This fibrous tissue contained distended blood vessels and polymorphonuclear leukocytes. The serosal surface was covered with fibrin and polymorphonuclear leukocytes. The marginal epithelium showed a slight downgrowth along the margins of the ulcer.

Fig. 1 (dog 19).—Early formation of ulcer.

Dog 19.—The stomach contained a small indurated ulcer on the lesser curvature involving the pyloric ring. The mucosa around this area was drawn together in purse-string fashion. A similar ulcer was located on the posterior wall about 2 cm. from the pyloric ring. Multiple superficial erosions were also present. Microscopic section of one of these erosions showed destruction of the mucous membrane and some involvement of the submucosa. The muscularis was not involved. The entire area was surrounded with polymorphonuclear leukocytes and lymphocytes, but showed no fibrosis. Microscopic sections from this stomach showed what is believed to be one of the earliest stages of gastric ulcer. One long crypt extended to the muscularis and ended in a flattened dilatation. The columnar epithelial cells covering the part resting against the muscularis were necrotic and covered with a layer of fibrin and polymorphonuclear leukocytes. Radiating from this area into the underlying tissue there were numerous polymorphonuclear leukocytes and a few large cells with a clear cytoplasm and a single vesicular nucleus. The vessels in this area were distended with blood (fig. 1).

The first portion of the duodenum showed an ulcerated area on the posterior wall measuring 6 by 12 mm. This ulcer was firm, had a necrotic base and on section showed some degree of fibrosis associated with a zone of inflammation. On the lesser curvature of the stomach, slightly posterior and adjacent to the pylorus, was a large indurated ulcer, 2 by 4 cm. in size, which had penetrated almost completely through the wall of the stomach. It had a necrotic base; its proximal and lateral borders were fairly smooth and undermined, and the distal border showed the familiar terraced appearance.

Mucicarmine stains on all sections showed a relative deficiency of mucin compared with sections taken from the same relative locations in the stomachs of normal dogs.

Fig. 2 (dog 23).—Chronic gastric ulcer with perforation.

Dog 23.—In the lesser peritoneal cavity there was a small circumscribed area of inflammation of the serosal coat of the stomach which was bound down by adhesions to the adjacent peritoneal surfaces. On tearing these adhesions, a quantity of foul-smelling fluid escaped from the stomach. In the stomach opposite this there was a large ulcer, 2 by 4 cm. in size, which had eroded completely through the wall of the stomach, but perforation had been prevented by protective adhesions. The ulcer showed overhanging edges, especially in the distal portion. Numerous eroded thrombosed blood vessels were visible in the base of the ulcer. In the fundus and along the lesser curvature there were several superficial erosions. The duodenum contained one slightly indurated ulcer on the posterior wall, proximal to the ampulla of Vater (fig. 2).

COMMENT

From the foregoing results it is apparent that cinchophen exerts a markedly deleterious influence on the gastro-intestinal tract of the dog.

This may be a species-selective action, but the reported clinical cases of cinchophen poisoning show symptoms referable to the gastro-intestinal tract. Schroeder described pyrosis, nausea, vomiting, diarrhea and anorexia in patients taking cinchophen. Apparently, then, the drug does not produce gastric disturbance in dogs only. Unfortunately, interest in the human cases reported has been centered on the liver, and little has been said of the gastro-intestinal tract.

Advantages of Method for Production of Ulcers.—Apart from the possible clinical application, the production of gastric and duodenal ulcers by the administration of cinchophen makes available a new approach to the experimental study of the formation of ulcers.

Eighty per cent of this series of twenty-four dogs acquired gastric ulcers, a lesion that occurs spontaneously with extreme rarity and has been produced experimentally with considerable difficulty in dogs. This number is as high as, or higher than, the number of ulcers produced by any other method hitherto reported. The five dogs that showed no ulcers ate the drug at infrequent intervals over a long period of time. Dog 5 had 8 doses over a two months' period. Dog 6 had 3 doses in twenty days. Dogs 9 and 24 had only 6 and 3 doses, respectively, and although the drug was administered regularly the dose and the total amount given were very small. Dog 7 had 10 doses in one hundred and thirty-seven days. It is apparent, then, that cinchophen, if given regularly over a sufficient period of time, will produce ulcers in almost 100 per cent of dogs.

From the reports in the literature the production of chronic gastric ulcer has been difficult, and the results have been variable. The one exception to this is the prolonged use of the roentgen ray as reported by Wolfer. Intestinal ulcers have been produced in a large percentage of dogs by use of the Mann-Williamson duodenal drainage operation or its modifications. These operative procedures disturb the normal anatomic relationship of the gastro-intestinal tract and consequently the physiologic relationship. Chronic gastric and duodenal ulcers in animals have not hitherto been produced by any of the mechanisms that operate in the formation of human peptic ulcers. By cinchophen feeding the normal anatomic arrangement is not disturbed, and thus the confusing factors that may result from trauma and from the malposition of these organs are eliminated.

Theories as to Pathogenesis.—The mechanism by which these ulcers are produced by cinchophen has not been determined. The possibilities suggested by these experiments are: 1. Cinchophen may have a direct toxic action on the gastric mucosa, combined with digestion by gastric secretions. 2. The drug may combine with the mucin of the stomach and thus remove the normal protection of the gastric mucosa. 3. It

may act on the autonomic nervous system and induce erosions by its neurogenic effect. 4. Cinchophen may influence the secretion of gastric juice, either directly or through the endocrine system. 5. The drug may have a general toxic action which affects the stomach directly or by causing metabolic disturbances as a result of its effect on the liver or pancreas. 6. The nutritional disturbances resulting from the anorexia that follows the ingestion of cinchophen may be a factor in the production of the ulcers.

Work is now in progress to determine, if possible, which of these factors is responsible for the production of gastric and duodenal ulcers in dogs fed with cinchophen.

SUMMARY

Acute and chronic gastric ulcers were produced in nineteen of twenty-four dogs. In four of these dogs ulcers were also found in the duodenum.

The five dogs in this series in which gastric ulcers did not develop were either fed inadequate doses or administered doses were distributed irregularly over such a long period of time that this effect of the drug was lost. Apparently, then, if cinchophen is given regularly to dogs over a sufficient length of time, gastric ulcers will result in practically all the animals.

The dose of cinchophen producing ulcers in all dogs is from 0.11 to 0.22 Gm. per kilogram per day.

The acute gastric ulcers were distributed widely over the gastric mucosa; 90 per cent of the chronic gastric ulcers were along the gastric pathway, or "Magenstrasse."

The duodenal ulcers were located above the ampulla of Vater and, in one case, occurred on both the anterior and the posterior wall.

The acute and chronic ulcers of both the stomach and the duodenum were identical with human peptic ulcers in their gross morbid anatomy and histology.

Laboratory Methods and Technical Notes

TWO-COLOR PHOTOMICROGRAPHIC LANTERN SLIDES FROM ORDINARY MATERIALS

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The usefulness of photomicrographic lantern slides in color for the demonstration of histologic details is universally conceded, but the technical difficulties in the production and projection of such slides deter many from their use. Of all the appliances used in color reproduction, none equals the screen plate in convenience or excels it in the faithfulness with which colors are recorded. For viewing as transparencies or for color reproduction, plates of this type are of the greatest value. Very satisfactory lantern slides may be made also by their use, but difficulties arise in their projection, since the color screen absorbs from 85 to 90 per cent of the light. In order to form a sufficiently brilliant image on the projection screen, it is necessary that a source of intense light be employed. Hence, these plates are poorly suited for projection in company with ordinary black and white plates, since an intensity of light that is barely satisfactory for the screen plates gives a painfully bright image with the usual monochrome slide.

Color separation methods in which separate color positives are superimposed for projection have long been known, and such procedures form the basis of color process commercial printing and color cinematography.

Full color reproduction requires the use of three color images. However, if the specimen to be photographed can be rendered in two colors, the use of tricolor methods is obviously extravagant. The majority of the sections of tissues used by the pathologist are stained with red or blue dyes, or with combinations of these two colors. Thus complete color reproduction can be obtained by two-color methods, at once greatly simplifying the process. By properly standardizing the various procedures, it is possible to produce satisfactory lantern slides of such transparency that they may be intermingled with ordinary black and white slides without visual strain. Since the positives are prepared from a pair of negatives, an indefinite number of duplicates may be made. In addition, one of these negatives may be used for black and white prints.

METHOD

Illumination.—The carbon arc and the incandescent lamp are the chief sources of illumination used in photomicrographic work at the present time. Various types of automatic carbon-feeding devices are available and, with many of them, a fairly uniform arc can be obtained.

From the Department of Pathology, The University of Michigan.

Of the incandescent lamps available, the 6 volt ribbon filament lamp is probably the most satisfactory. If the light is used from a small portion of the filament, it is very uniform, while the intensity is adequate for any photographic purpose, provided that the condenser system is carefully set up.

The light for color work must be constant in intensity and composition. In these respects, the incandescent lamp is superior to the carbon arc light and also is far more convenient. For the most critical work, the lamp may be provided with an ammeter and rheostat, so that the operating conditions may be consistently reproduced. Where the voltage supplied is reasonably constant, such additional equipment seems to be an unnecessary refinement.

Optical System.—The entire optical system from the condenser to the ocular should be of the apochromatic type. It must be emphasized that color work with any but the most highly color-corrected lens systems available is a waste of time. With achromatic lenses which are satisfactory for visual work, the separate color images will not be formed in the same plane and of the same size, so that registration is impossible. Special attention should be given the ocular to insure that it is adapted to the particular objective used; otherwise the fine color corrections of both lenses may be impaired.

Photographic Material.—For several reasons, glass plates will be found more satisfactory for negatives than cut films, although the latter are more convenient to store. The rigidity of the base makes the glass plate free from distortion, and it may also be more conveniently handled in the subsequent placement of registration marks and in printing.

Panchromatic emulsions are a necessity. Of the many excellent plates available, the Wratten and Wainwright "M" plates are probably the most satisfactory. These are moderately rapid plates with an unusually fine grain and give practically any desired degree of contrast.

The plate should be 4 by 5 inches (10.16 by 12.7 cm.). This gives a generous margin about the lantern slide positive in printing, so that a slight movement of the camera back in changing plate-holders at the time of the exposure is of no importance. Since the prints are made by contact, any larger plate results in a waste of material.

For the positives, the Eastman slow lantern slide plates are used.

Exposure.—The plate-holders are loaded in absolute darkness, and one holder should have some marking device to cast a shadow on the corner of its plate. This may be a small metal strip tacked to the holder or a piece of paper pasted to the kit holding the plate. If the marked holder of each pair is always used with the same filter, the negatives can thus be easily distinguished.

The photomicrographic equipment having been set up in the usual way, a sharp image is focused on the ground glass in the size desired for the lantern slide. The image must be uniformly sharp and absolutely free from color fringes. When the image is satisfactory, the exposures are begun and no more adjustments of the camera or of the microscope are attempted. The shutter is closed, and a holder carrying a Wratten "F" filter is placed on the optical bench. This is a deep red filter, passing less orange than the usual tricolor red filter. A loaded plate-holder is inserted, the slide drawn and the exposure made. The plate-holder is removed, and without disturbing the camera in any way, the second holder is inserted, and the red filter is replaced by a combination of the Wratten "B" and "H" filters. These filters together give a pure green and are practically opaque to red light. The second exposure is then made by green light, and the plates are ready for development.

The time of exposure must be determined by experiment and will depend on the intensity of the light on the ground glass, the composition of the light before it is filtered, the position of the filter (which should be between the field and substage condensers) and the sensitivity characteristics of the emulsion used. Test exposures should be made with each filter in the following manner: For the red light exposure, the slide is withdrawn and an exposure of one second is given; the slide is inserted part way across the plate, and another exposure of one second is made; the slide is pushed farther in and two seconds' exposure given and again one of four seconds, doubling each time. In this way, a series of strips is formed on the negative, the successive total exposures being: one, two, four, eight, sixteen, thirty-two, etc., seconds. The same procedure is employed with the green filter combination save that here it is advisable to start with fifteen seconds, as the light through these filters is much less intense. These plates, after being developed simultaneously, may be examined and the exposures giving comparable and satisfactory densities selected. If objects of a gray color appear in the section, these should have the same rendering in both negatives, with correct exposures.

Development.—Color negatives should be quite soft with delicate tonal gradation. It is best to develop the pairs of plates simultaneously, using a tank. Of all the developing solutions tried, the Eastman borax developer D-76 is by far the most satisfactory, and this procedure is partly based on the use of this solution.

(Eastman D-76 developer [1] is prepared as follows:

Elon	4 Gm.
Sodium sulphite	200 Gm.
Hydroquinone	10 Gm.
Borax	4 Gm.
Water	2 liters

Dissolve the elon separately in a small volume of water [125 F.]. Then dissolve approximately one fourth of the sulphite separately in hot water [160 F.]. Add the hydroquinone with stirring until completely dissolved. Then add this solution to the elon solution. Now dissolve the remainder of the sulphite in hot water [160 F.]. Add the borax, and when it is dissolved, add the mixture to the aforementioned solution. Dilute to volume with cold water.)

Exposure is adjusted to give satisfactory density in six minutes at 65 F. (18 C.). The development can be done in total darkness by time and temperature alone or, better, the plates may be given a preliminary desensitizing bath of 1:10,000 pinakrytol green for two minutes. The cage containing the plates is immersed in the desensitizing bath in total darkness for the required time, drained, and then placed in the developer. After about two minutes, a rather bright ruby light can be turned on with no risk of fog, although it is best to give the plates no unnecessary exposure to light. The time and temperature method can thus be supplemented by direct visual examination and underexposure or overexposure partially corrected in development. On completion of development, the cage with the plates can be transferred to the rinsing water and thence to the fixing bath, so that they need not be handled individually until they are ready for the final washing.

Registration Marks.—After the negatives are dry, registration marks are placed on them so that the lantern plates may be properly placed in position when printing. A lantern slide cover glass or a spoiled lantern slide plate from which

1. Eastman Professional Films, Rochester, N. Y., Eastman Kodak Company, p. 17.

Fig. 1.—Photomicrograph of a myocardial lesion, × 200; hematoxylin and eosin stain. This print is made from the blue-printing negative, exposed by red light. The black area is the shadow cast by the marking device in the plate-holder. The registration marks have been inked over to give them greater prominence.

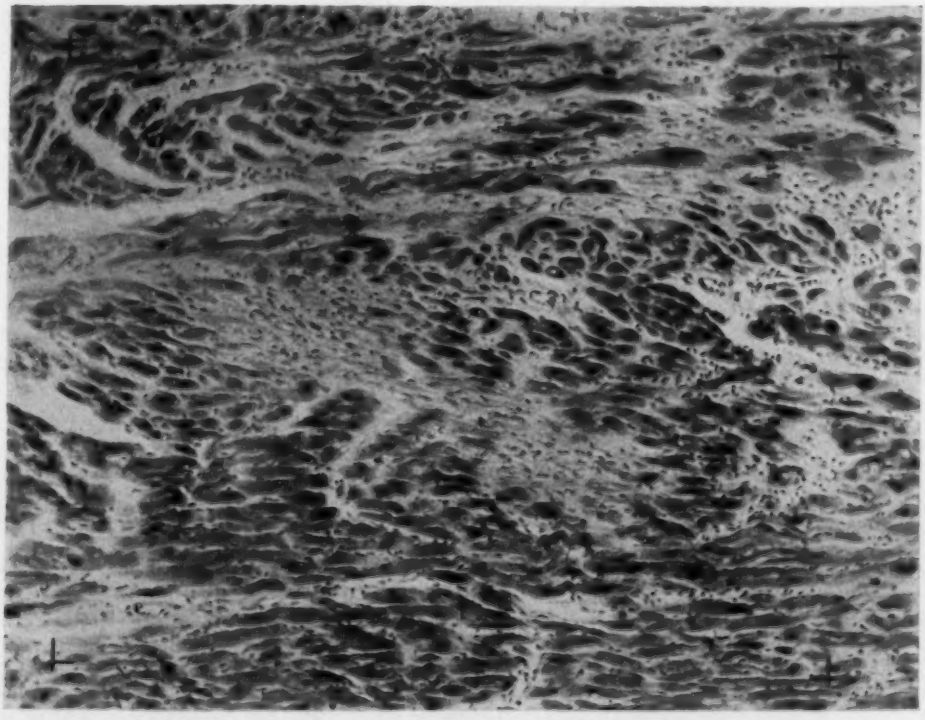

Fig. 2.—Print from the red-printing negative of the same area as figure 1. Exposure was made by green light. This negative is also satisfactory for black and white reproductions on paper, or for black and white lantern slides.

the emulsion has been removed is placed over one of the negatives, which is allowed to lie emulsion side up on a glass surface illuminated from below. The lantern plate is adjusted so that the field desired is properly centered, and two points are selected that appear in both negatives and their positions are indicated by tiny dots of ink placed on the registration plate. These points may be nuclei, artefacts or any definite structures that are clearly shown in both negatives.

While the plates are held firmly in position, a sharp scalpel is used to make cuts in the negative emulsion outlining the corners of the registration plate. This is then transferred to the second negative, its position being determined by aligning the ink dots with the previously chosen points in the negative, and similar cuts are made in the emulsion of this negative at the corners of the plate (figs. 1 and 2). In printing, it is necessary only to place the lantern slide plates with their corners coinciding with the intersections of the cuts to obtain close registration, which may be made exact by a very slight shifting of the two positives in mounting.

Printing.—Blue Image: The negative made through the red filter is used to make the blue image and should be marked with the word blue, so that confusion will not result in the printing room. The blue image is obtained by first making a *thin* black and white slide in the usual way. By holding the negative up to the ruby light the lantern slide can be accurately placed by means of the registration cuts in the emulsion. The negative and positive plates are put together, emulsion to emulsion, and the exposure made with a 25 watt lamp at a distance of about 10 feet (3 meters). The exposure should be adjusted so that development takes at least two minutes, giving a thin but rather brilliant slide.

After the slide has been fixed and washed, the silver image is toned blue by the iron toning process.

(The iron toning solution T-11 [2] is prepared as follows:

Ammonium persulphate	0.5 Gm.
Iron and ammonium sulphate (ferric alum)	1.4 Gm.
Oxalic acid	3.1 Gm.
Potassium ferricyanide	1.0 Gm.
Ammonium alum	5.2 Gm.
Hydrochloric acid 10 per cent	1 cc.
Water to make	1 liter

Each of the solid chemicals should be dissolved separately in a small quantity of water and the solutions then mixed strictly in the order given, and the whole diluted to the required volume. The bath will be pale yellow and perfectly clear.)

Toning is complete in from five to ten minutes, and there is a moderate intensification; hence, the necessity for having a thin slide with clear whites to start with. After being washed for ten minutes and dried, the blue plate is completed.

Red Image: The negative made through the green filter combination is used to produce the red plate. Here no satisfactory red-toning procedure is available that surpasses the printing on bichromatized gelatin. Ordinary lantern slide plates have a soluble emulsion that is ideal for this method of printing and, in addition, the plates are more uniformly coated than are most of those coated by amateurs. The plates are sensitized by bathing for five minutes in the following solution:

Ammonium bichromate	30 Gm.
Strong ammonia	5 cc.
Water	1 liter

2. Lantern Slides, Rochester, N. Y., Eastman Kodak Company, p. 27.

The temperature of the bath should not exceed 65 F. (18 C.); otherwise the gelatin may develop reticulation. After a quick rinse in distilled water to remove the excess of the sensitizing solution, the plates are dried in the dark in a current of air. When dry, they are sensitive to white light, but may be handled safely in a bright orange light or a subdued artificial light.

With these plates, the printing must be through the back and by the light of the carbon arc. The lantern slide plate is placed with the back in contact with the emulsion of the red-printing negative and its position adjusted by means of the registration marks. Since now the thickness of the plate intervenes between the negative emulsion and the bichromatized gelatin, printing must be done with parallel rays in order that sharp rendition may be obtained. The arc is therefore placed at the focal point of a condensing lens at least as large as the printing frame so that the negative surface makes a right angle with the light rays. The time of exposure will vary from thirty seconds to several minutes, depending on the density of the negative and the intensity of the arc. A fair judgment of the exposure may be obtained by examining the positive plate from the emulsion side. With proper exposure, the image will be fully visible.

Development is accomplished by immersing the exposed plate (emulsion side up) in a tray of warm water at a temperature of about 125 F. (52 C.). With gentle rocking, the unexposed gelatin begins to dissolve in about one minute. Development is continued until the image appears clearly defined and no more gelatin appears to be dissolving. Owing to the silver salt, which here acts as an inert pigment, the image is sharply visualized in all its tonal gradations. If the plate has been underexposed, the high light detail will be lost, while if it has been overexposed, the gelatin will not dissolve sufficiently to make possible a clearing of the high lights. Development will be complete in from five to eight minutes.

Since the silver halide is of no further use, it is removed and the gelatin hardened by immersion in a chrome alum fixing bath. If any particles of sediment form, they may be removed by gently swabbing the plate with a tuft of cotton during washing. After fixation and washing, the plate will appear perfectly clear, and it will be only by using oblique lighting that the image can be perceived. Staining of the image may be done immediately, or the plate may be dried and stained subsequently.

A 1 per cent aqueous solution of eosin is used for staining. If less rapid and somewhat more brilliant staining is desired, the solution may be acidified with acetic acid. In general, moderate overstaining followed by sufficient washing to clear the high lights will be found to give a very satisfactory brilliance. After drying, the plate is ready to be mounted.

Concerning the intensity of staining desired, it is impossible to give explicit directions; only actual experiment will suffice. In the beginning it is well to make the positives in a color intensity series, and by trying various combinations in the lantern the proper balance will be perceived quickly. Subsequent positive pairs are then made in equivalent color intensity.

Mounting.—One of the plates is placed emulsion side up on the table and a small drop of hard Canada balsam placed at each of two diagonally opposed corners. A thin, ready-cut mask is placed in position, and two more drops of balsam are placed on the mask at the same corners. The second plate is lowered face down in the proper position for registration. The pack is then lifted and, while held in the fingers, the plates are adjusted until registration is exact. When they are in the correct relationship, the assembly is clamped in a lantern slide-vise, and the edges are bound as usual. Plates bound in this manner will not slip even with rough handling.

SUMMARY

The foregoing procedure has been developed, not as a unique contribution to the subject of color reproduction, but as a method by which any one with moderate photographic skill can produce excellent lantern slides in color without being forced to purchase expensive specialized materials. Slides prepared in this manner have a high degree of transparency together with precise rendition of fine detail. By relatively slight modifications, the method can be extended to the reproduction of two-color combinations other than red and blue. Finally, only standardized materials, with which the photographer is familiar, are employed.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths.—William Ophüls, professor of pathology in the school of medicine of Stanford University, San Francisco, has resigned as dean of the school after sixteen years of service.

Julius Klosterman is assistant professor of bacteriology and pathology in New York University.

Howard T. Karsner, professor of pathology in Western Reserve University, has been elected a member for the United States of the executive committee of the International Society for Geographic Pathology.

James H. Peers has been appointed instructor in pathology in the school of medicine of Boston University.

Georg Schmorl, prosector and director of the pathologic institute of the Stadtkrankenhaus Friedrichstadt in Dresden, until April 1, 1932, died on August 14, at the age of 71. While preparing a spinal column he scratched a finger and died of streptococcal septicemia after an illness of eleven days. His favorite subject of study for many years was bone pathology, most recently the vertebrae and intervertebral disks in particular. He had been secretary of the German Pathological Society since 1903.

William B. Brebner, assistant professor of bacteriology, University and Bellevue Hospital Medical College, died on November 9, at 29 years of age, from transverse myelitis, which followed the bite of a monkey.

New York State Requires Tissue Examinations.—The state public health council, at a meeting on September 23, added to the sanitary code a new regulation requiring that tissue removed at operation or necropsy for examination must be submitted to an approved laboratory, to the division of laboratories and research in Albany or New York or to the state institute for the study of malignant diseases at Buffalo. The new rule, which applies to all examinations made to aid in the diagnosis, prevention or treatment of disease or to determine the cause of death, takes effect on Jan. 1, 1933.

Society of American Bacteriologists.—At the annual meeting in Ann Arbor, Mich., from December 28 to 30, inclusive, the tercentenary of the birth of Anton van Leeuwenhoek will be commemorated by a historical exhibit of Leeuwenhoekiana. Round table discussions will be held on (1) bacterial filtrability, dissociation and life cycles, (2) microbiology of frozen foods and (3) taxonomy.

Scientific Exhibit, Milwaukee Session of American Medical Association.—Application blanks are now available for space in the Scientific Exhibit at the Milwaukee Session of the American Medical Association, June 12 to 16, 1933. The final date for filing such applications is Feb. 13, 1933, after which time assignments of space will be made. The Committee on Scientific Exhibit requires that all applicants fill out the regular application form. Persons desiring to receive application blanks should address a request to the Director, Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE RELATION OF HEART WEIGHT TO THE BASAL METABOLISM AS VARIED BY THYROID ADMINISTRATION. F. M. SMITH and E. M. MACKAY, J. Exper. Med. **55**:903, 1932.

A linear relationship exists in the albinic rat between the heart weight and the basal metabolic rate when varied by the administration of active thyroid material. It is suggested that this increase in heart weight which follows the increase in metabolism after the administration of thyroid is in the nature of a simple work hypertrophy of the myocardium. AUTHORS' SUMMARY.

THE ANEMIA OF SCURVY. S. R. METTIER and W. B. CHEW, J. Exper. Med. **55**:971, 1932.

Loss in weight, progressive anemia and moderate increase in reticulated red blood cells occurred in seventeen guinea-pigs on a diet deficient in vitamin C. The bone marrow of the guinea-pigs with scurvy showed large numbers of erythrogenic cells, but scant evidence of active maturation to adult erythrocytes. A reticulocyte response was induced in guinea-pigs with scurvy when they were fed orange juice daily. During the reticulocyte response, the bone marrow showed large numbers of mitotic figures and relatively more adult red blood cells than did the bone marrow of guinea-pigs with scurvy that had not been treated with orange juice. It is concluded from this study that the anemia of guinea-pigs with experimentally induced scurvy is largely dependent on a deficiency of vitamin C resulting in retarded maturation of the red blood cells. AUTHORS' SUMMARY.

BILE PIGMENT AND CHOLESTEROL IN THE GALL BLADDER BILE OF THE DOG. C. RIEGEL, C. G. JOHNSON and I. S. RAVDIN, J. Exper. Med. **56**:1, 1932.

The data obtained from the experiments on dogs reported in this paper lead us to conclude that bile pigment is not absorbed from the bile of the gallbladder. The mean loss of pigment is so small when compared with the amount of water lost that it is negligible. Our data on cholesterol do not support the concept that this substance is secreted into the bile of the gallbladder under normal conditions. In the majority of experiments there was a loss of cholesterol. Indeed, we have failed to find any evidence of definite secretion or absorption save in the case of the infected gallbladder. We are led to conclude, as did Rous and McMaster with regard to bile pigment, that normally there is no absorption of cholesterol. AUTHORS' SUMMARY.

FIXATION BY THE INFLAMMATORY REACTION. V. MENKIN, J. Exper. Med. **56**:157, 1932.

The results of this study furnish evidence, in addition to that already provided, that fixation of foreign substances is primarily due to mechanical obstruction by a fibrin network and by thrombosed lymphatics at the site of inflammation. The significance of fixation in relation to immunity and its bearing on some of the other processes involved in the inflammatory reaction are stressed.

AUTHOR'S SUMMARY.

PERMEABILITY OF THE LYMPHATIC CAPILLARY. S. HUDACK and P. D. MCMASTER, J. Exper. Med. **56**:223 and 239, 1932.

A technic was developed for the demonstration of lymphatic capillaries in the ear of the mouse by means of vital dyes and for tests of their permeability under normal and pathologic conditions. The lymphatics became visible as closed channels from which the dyes escaped secondarily into the tissue. Some of them, cross-connections, with extremely narrow lumens, seemed ordinarily not to be utilized. There was active flow along the lymphatics of the ear of the mouse under ordinary circumstances. The movement of dye was always toward the main collecting system. The valves of the lymphatics as well as the flow of the fluid prevented distal spread. There was, in addition, slow migration, apparently interstitial, but in the same general direction, of dots of color produced by the local injection of dye. The normal permeability of the lymphatics was studied with dyes of graded diffusibility. Their walls proved readily permeable for those highly diffusible pigments that the blood capillaries let through easily, but retained those that the latter retained. Finely particulate matter(india ink, *"Hydrokollag"*) they did not let pass. No gradient of permeability was observed to exist along them such as exists along the blood capillaries of certain organs. The observed phenomena of lymphatic permeability, like those of the permeability of the blood capillaries, can be explained on the assumption that the lymphatic wall behaves like a semipermeable membrane.

A standardized solution of a vital dye which escapes with some difficulty from the lymphatics of the ear of the mouse was utilized in tests of the permeability of the lymphatic wall under various conditions. It was found that this permeability is subject to great change. Slight pressure that sufficed to prevent lymph flow from the ear—an organ in which such flow goes on normally—soon resulted in increased permeability of the obstructed lymphatics without any perceptible dilatation of these vessels. Mechanical stimulation—for example, a stroke with a blunt wire or scratching so light as not to break the epidermis—resulted in a practically immediate great increase in lymphatic permeability, which was sharply localized to the region pressed on. This increase in permeability, though so great that even hemoglobin was let pass by the lymphatics, endured but a few hours. Warming the ear to 43 C. or exposure to mild sunlight increased permeability considerably. Slight chemical irritation increased it greatly, though not so much that particulate matter was allowed to pass. The edema developing as a result of lymphatic obstruction or of mechanical, thermal or chemical stimulation was preceded by and associated with a large increase in lymphatic permeability. The facts are discussed in relation to their bearing on the accumulation of fluid within the tissue. It is plain that influences within the realm of the normal suffice to increase lymphatic permeability, and that those which lead to edema cause a very great increase in it. In proportion as this increase occurs, the lymphatics cease to be channels demarcated by a semipermeable membrane. It seems certain that the changes must be in some part responsible for the local accumulation of fluid. There exist possibilities, on the other hand, of a correlation between the functionings of the blood and lymph vessels under certain pathologic conditions, as during the resorption of edema.

AUTHORS' SUMMARIES.

THE INFLUENCE OF AGE ON COMPENSATORY RENAL HYPERTROPHY. E. M. MACKAY, L. L. MACKAY and T. ADDIS, J. Exper. Med. **56**:255, 1932.

Compensatory hypertrophy of the kidney in albinic rats becomes less as age advances. There is a rapid decrease at from 5 days to 60 days of age, and then a slow diminution throughout adult life.

AUTHORS' SUMMARY.

THE PRODUCTION OF OSTEOGENIC SARCOMA AND OTHER CHANGES FROM RADIOACTIVE MATERIAL INJECTED INTO RABBITS. F. R. SABIN, C. A. DOAN and C. E. FORKNER, J. Exper. Med. **56**:267, 1932.

The observations in this work suggest that, with certain doses of radioactive material, the fundamental damage in the lymphoid tissues is to the stem cell, and

that the damage is to the chromatin of the nucleus of the cell. The erythroid tissues are apparently less susceptible to damage by radioactive material than the lymphoid tissues, but an original anemia of secondary type from peripheral destruction may eventually be changed to one of primary type through decreased maturation of primitive cells in the marrow. The damage of lymph nodes and bone marrow leads to atrophy of these organs. The cells of the liver and thymus suffer nuclear damage of the same general character as is seen in the lymph nodes, and there is atrophy of these organs. The storage of the radioactive material in the bones gave rise to osteogenic sarcomas in two of seven rabbits surviving from eleven to nineteen months. A repetition of the experiment has been undertaken with more intensive studies to test the validity of the findings.

AUTHORS' SUMMARY.

GEOGRAPHIC PATHOLOGY OF GOITER. C. A. HELLWIG, Surg., Gynec. & Obst. **55**:35, 1932.

No modern American treatise on diseases of the thyroid gland refers to the variations in form and function of goiters according to the part of the country in which they occur. From the few facts which are known it would appear that North American goiters do not vary in different regions as widely as do European. The few statistical data available for North America seem to indicate that the goiters observed in this country are rather uniform, but very different from those in regions of high endemicity (Switzerland, Himalayas, Pyrenees). In Kansas and Wisconsin in surgical patients, there are more diffuse than nodular goiters. In North American surgical material, the diffuse and nodular colloid goiters are the most common (from 68 to 79 per cent). Tyreotoxic symptoms, accompanying goiter, are more frequent in this country than in any other so far studied (70 per cent of the surgical cases). For a systematic comparison of the morphology and physiology of goiters in many different areas of North America, the acceptance of a uniform classification appears essential. Aschoff's classification, which, in 1927, at the International Goiter Conference in Bern found the unanimous consent of all leading students of goiter, is recommended.

AUTHOR'S SUMMARY.

CORTICAL PROLIFERATION IN THE MOUSE SUPRARENAL AFTER PEPTONE. RAYMOND WHITEHEAD, Brit. J. Exper. Path. **13**:200, 1932.

Intraperitoneal administration of Witte's peptone in maximal doses to mice was followed by abnormal proliferation in the suprarenal cortex. Mitosis first became appreciable fifty-six hours after dosing, was maximal between seventy-one and eighty-two hours thereafter, and was declining at ninety-seven hours. Mitoses were most numerous in the outer part of the cortex. In its inner part, they were very rare. Dispirems far outnumbered the other phases of mitosis, which in order of decreasing frequency were monospirems, monasters and diasters. Mitosis was as a rule most active in mice showing the least departure from the normal in temperature, general condition and weight. Both morphologic and clinical evidence supports the view that the mitoses seen in the suprarenal cortex after the administration of peptone are probably an indication of active function.

AUTHOR'S SUMMARY.

EXPERIMENTAL NEPHRITIS PRODUCED BY THE STYRYL QUINOLINE COMPOUND NO. 90. H. L. SHEEHAN, J. Path. & Bact. **35**:589, 1932.

A styryl quinoline compound, no. 90, produces acute nephritis on injection into rabbits. This is characterized by necrosis of entire first convoluted tubules chiefly in the outer parts of the cortex, followed by regeneration of the tubular epithelium. After about nine days, fibrosis develops around the regenerated tubules, which then gradually atrophy and disappear. The glomeruli remain intact in the resultant scars for about six months and then become fibrosed by a process similar to ischemic atrophy. In those animals that live for over two months after moderately

severe nephritis, the blood urea is permanently slightly raised, but the concentrating power of the kidneys becomes normal. When a harmless dose of no. 90 is given, the dye is taken up directly from the blood stream by the epithelium of the first convoluted tubules and of the broad ascending limbs of Henle. This absorption depends on the physiologic activity of the cells of the tubules and is inhibited by previous damage to them. The manner of excretion suggests that about half of the dye taken up by the cells of the tubules at the beginning is secreted into the lumen of the tubules in the course of the next twenty-four hours; the remainder disappears, possibly as a result of intracellular destruction. When a nephrotoxic dose is given, the process of adsorption and excretion appears to be the same, but the cells are damaged by the large amount of dye which they accumulate in their cytoplasm. The excretion in the urine is decreased in proportion to the extent of the lesions, and there is thus a prolonged retention of this large amount of dye in the cells, which probably continues and completes the initial damage.

AUTHOR'S SUMMARY.

Pathologic Anatomy

ARTHRITIS DEFORMANS OF THE SACRO-ILIAC JOINTS. F. ZOELLNER, Virchows Arch. f. path. Anat. **277**:817, 1930.

Examination of the sacro-iliac joints in sixty cadavers revealed frequently arthritis deformans. Owing to the anatomic peculiarities of this joint, the pathologic picture of the disease is somewhat different from that in other joints. Exulcerations of the cartilage are usually absent. The proliferating vessels of the bone marrow entering the damaged cartilage frequently cause occlusion of the joint space. This is followed later on by cartilaginous adhesion and finally by true ankylosis.

W. SAPHIR.

THE HISTOLOGY OF ACUTE RHEUMATIC FEVER. F. KLINGE, Virchows Arch. f. path. Anat. **279**:1 and 16, 1930.

In a previous communication, Klinge described, as the earliest tissue reaction in acute rheumatic infection, fibrinoid degeneration of connective tissue, with edematous dissociation of connective tissue fibrillae and death of connective tissue cells. This process occurs in connective tissue throughout the body and has been noted by him in the tonsils, myocardium, pericardium, endocardium, blood vessels, muscles, tendons, joints and hepatic and splenic capsules. The reaction is a focal one. In two consecutive papers, he now describes the intermediate or subacute stage of the reaction and the terminal stage. The primary, degenerative stage of tissue reaction is followed by proliferation of connective tissue, with the formation of the characteristic rheumatic granulomatous nodule. This, too, is a temporary stage in the rheumatic tissue reaction. In time the cells of the nodule degenerate and disintegrate, the replacing connective tissue differentiates, and the nodule becomes transformed into a scar, which in rare instances may undergo calcification or ossification. Klinge attempts to differentiate between clinical and anatomic recidives in rheumatic infection. By clinical recidive he understands an exact repetition of the three stages in the pathologic process after an interval of freedom from the disease. By anatomic recidive he understands the development of more recent reactions in the scars of older lesions or the presence of all three stages of the pathologic process in the same case.

W. SAPHIR.

ORIGIN OF THE MIGRATORY CELLS OF ACUTE INFLAMMATION. F. FREUND, Virchows Arch. f. path. Anat. **279**:30, 1930.

In the acute traumatic inflammation of the tongue of the living frog, in the experiment devised by Cohnheim, the presence of many large wandering cells is noted. These, according to Freund's observations, do not come from the blood but are derived from the connective tissue.

W. SAPHIR.

FACTORS INFLUENCING LEUKOCYTIC EMIGRATION IN ACUTE INFLAMMATION. M. NORDMANN and A. REUTLER, Virchows Arch. f. path. Anat. **279**:45, 1930.

The observations reported were made on the mesentery of the living rabbit infected with colon bacilli. The parietal or marginal localization of the leukocytes within the vessels, which is a prerequisite for leukocytic emigration, is dependent on retardation of the blood flow and decreased excitability of the local vasoconstrictors. Leukocytic emigration can be suppressed by preventing retardation of the blood flow by means of drugs that cause local vasodilatation, such as cocaine or atropine, or by causing a general hypertension through elimination of the mechanism regulating blood pressure.

W. SAPHIR.

DIFFUSE HEMANGIOMATOSIS OF THE SPLEEN. A. A. WASSILJEFF and A. W. PROTASSEWITSCH, Virchows Arch. f. path. Anat. **279**:79, 1930.

Cavernous hemangioma of the spleen may occur as a single cavernoma, as multiple cavernomas and as diffuse hemangiomatosis. The last named is the rarest, only a few examples being recorded in the literature. The authors' example occurred in a man, aged 32, who had an enlarged spleen and no significant laboratory findings. Splenectomy was done, and the patient left the hospital in good condition in three weeks. The large, congested spleen revealed a few pea-sized cavities. Microscopically, the spleen was transformed into hemangiomatous cavities of variable size. They contained a colloid-like material, little blood and deposited iron and calcium salts. The spaces were surrounded by and separated from each other by thick walls of connective tissue. The authors believe that the colloid contents of the spaces were derived from the contained blood.

W. SAPHIR.

VASCULAR GRANULOMAS OF THE PLEURA SIMULATING ECCHYMOSES. G. KOHLSCHUETTER, Virchows Arch. f. path. Anat. **279**:85, 1930.

Subpleural ecchymoses of larger or smaller size are frequently seen when death is due to passive congestion, suffocation or acute sepsis. Such ecchymoses may be confused with lesions of similar gross appearance, but of entirely different histologic structure. The lesions that Kohlschuetter describes occur as bluish or black, slightly elevated, circular or elliptic spots of variable size. They may be few in number and then are usually located near the interlobar fissure, or they may be numerous and scattered over the entire visceral pleura. They are composed of granulation tissue containing numerous capillary blood vessels and mononuclear lymphoid cells, the latter often aggregated about the vessels. Blood pigment or other evidence of previous hemorrhage has never been seen by Kohlschuetter. He believes that the lesions arise as the result of minute ruptures of the pleura due to spells of coughing caused by chronic bronchitis. Prolapse of pulmonary tissue through the minute ruptures occurs, and this is followed by reparative inflammatory reactions, which lead to the formation of the lesions described. Because of their similarity to subpleural ecchymoses, they may have medicolegal importance.

W. SAPHIR.

EXPERIMENTAL REGENERATION IN TISSUE CULTURE. A. FISCHER, Virchows Arch. f. path. Anat. **279**:91, 1930.

Regeneration in tissue culture bears a close resemblance to that of healing wounds. Fischer made wounds in tissue cultures by excising a central area or a sector from the periphery. Regeneration of tissue immediately set in at the margin of the wound. The speed of the regenerative process was independent of the nutritive conditions of the culture, but was proportional to the age of the culture. The number of mitoses at the margin of the wound was identical with that at the growing periphery of the culture. The speed of the regenerative growth was

increased as compared with that of the control culture. This was probably due to substances that developed after the wound had been induced, and that were capable of promoting growth. This explanation is supported by the fact that tissue cultures subjected to repeated wounding grew at a markedly greater rate than the control cultures.

W. SAPHIR.

INTESTINAL LYMPHOGRANULOMATOSIS. W. NOWICKI, Virchows Arch. f. path. Anat. **279**:146, 1930.

Nowicki gives a thorough review of the literature of primary isolated lymphogranulomatosis and presents a case of his own. A man, aged 36, died with symptoms of intestinal obstruction. Necropsy showed stenosis of the ileum, due to an infiltrative thickening of the wall that narrowed the lumen. The tissue had the histologic characteristics of cellular lymphogranulomatous tissue. No other evidences of the disease elsewhere could be detected.

W. SAPHIR.

HISTOLOGY OF FOLLICULAR KERATOSIS (DARIER'S DISEASE). H. HAMLI, Virchows Arch. f. path. Anat. **279**:237, 1930.

This study of the chronic dermatosis described by Darier and named by him "dysceratose folliculaire" is based on material removed for biopsy. The characteristic alteration is hyperplasia of the basal cell layer of the epidermis, with lateral and downward ingrowth into the cutis. Concentric masses of the proliferated epithelium may become isolated in the cutis, forming the "corps ronds" of Darier, termed perloid bodies by Hamli. The clinical manifestations are due to extension in various directions and to regressive and regenerative, healing processes. In agreement with Andry, Hamli prefers the descriptive designation "pseudofollicular" to "follicular," since in all the lesions examined he has never seen primary involvement of the follicles.

W. SAPHIR.

ACANTHOSIS NIGRICANS WITH INVOLVEMENT OF THE ESOPHAGUS. H. TESSERAUX, Virchows Arch. f. path. Anat. **279**:244, 1930.

In a woman with the clinical diagnosis of carcinoma of the stomach, acanthosis nigricans of the skin developed three months before death. At necropsy there was found a carcinoma of the stomach, with metastasis to the regional lymph nodes. A circumscribed papillary lesion of the mucosa of the esophagus revealed, histologically, papillary hypertrophy of the submucosa, with round cell infiltration and marked thickening of the epithelial layer. The histologic picture was similar to that of the acanthotic lesions of the skin.

W. SAPHIR.

OBLITERATION OF THE THORACIC DUCT. A. FEHR, Virchows Arch. f. path. Anat. **279**:265, 1930.

In a woman, aged 50, with chylous ascites and chylous hydrothorax, necropsy revealed carcinoma of the stomach. The lymph vessels of the region were obstructed by carcinomatous thrombi. The thoracic duct was obliterated in the greater portion of its course. The obliteration was due to a condition termed by Fehr endolymphangitis productiva, which he believes was secondary to the carcinomatous obstruction of the radicles of the duct. Obstruction here was followed by proliferation of the intima of the main duct and by thrombosis within the narrowed lumen.

W. SAPHIR.

MUCOUS CYSTS OF THE KNEE JOINT. P. ZAECH-CHRISTEN, Virchows Arch. f. path. Anat. **279**:273, 1930.

Mucous cysts of the knee joint are rare. From a review of the literature and a study of four cases of his own, Zaech-Christen concludes that these cysts

arise from the outer border of the semilunar cartilage. Histologically, they are identical with the ordinary ganglion. The cysts are filled with a mucous fluid and are lined by a layer of flat cells of endothelial character. The cysts probably arise from the para-articular mesenchymal tissue, which proliferates as the result of irritation or stimulation. The proliferated tissue undergoes mucoid transformation, and in time a cavity is formed. Such cysts are not tumors, but are inflammatory malformations.

W. SAPHIR.

Microbiology and Parasitology

DERIVATION OF STAPHYLOCOCCUS ALBUS, CITREUS AND ROSEUS FROM STAPHYLOCOCCUS AUREUS. M. PINNER and M. VOLDRICH, J. Infect. Dis. **50**:185, 1932.

Apathogenic S. albus, S. citreus and S. roseus are split off spontaneously from pure line strains of pathogenic S. aureus. The splitting-off of S. albus can be much enhanced by growing S. aureus in broth containing S. aureus agglutinins and by animal passage. The three nonidentical strains derived from S. aureus appear to be stable under ordinary conditions. They differ from the mother strains in regard to pigment production, growth intensity, individual morphology, staining reactions, virulence, fermentative and proteolytic action, hemolysin production, alkali production, agglutinability, immunizing properties and susceptibility to bacteriophage. From albus strains aureus strains can be recovered by culturing the albus strains for prolonged periods in mediums containing high concentrations of anti-albus serum. The relation between aureus and albus strains is essentially similar to that between S and R strains of other micro-organisms.

AUTHORS' SUMMARY.

THE BACTERIOLOGY OF BRONCHIECTASIS. P. H. GREEY, J. Infect. Dis. **50**:203, 1932.

A uniform bacterial flora was not found in nine cases of bronchiectasis. Bacteria of various types were obtained in each of the cases studied. The absence of spirochetes in five of these cases suggests that their presence in the other four was a chance invasion. This also holds true for the other micro-organisms isolated. Pure cultures of a single type of streptococcus have been obtained from the bronchi following lobectomy on three occasions, which indicates that a mixed infection is not necessarily present. The variety of micro-organisms recovered suggests that no specific type plays an etiologic rôle, but that many bacteria are capable of producing bronchial damage sufficient to favor dilatation.

AUTHOR'S SUMMARY.

THE VIRUS OF HERPES. M. HOLDEN, J. Infect. Dis. **50**:218, 1932.

The enhanced resistance of desiccated herpes virus to deterioration, heat and the action of certain chemicals is striking when compared with the resistance of moist herpes virus to the same factors. A comparison of the resistance of pneumococci, both moist and dried, to chemical agents and heat, with the resistance of herpes virus under similar conditions, furnishes results that are not inconsistent with the assumption of the living nature of the virus.

AUTHOR'S SUMMARY.

THE EFFECT OF URINE ON HEMOLYTIC STREPTOCOCCI. G. H. ROBINSON and F. A. TAYLOR, J. Infect. Dis. **50**:249, 1932.

Dissociation of hemolytic streptococci by exposure of the organisms to urine is doubtful, or at least of rare occurrence, and cannot be controlled. Hemolytic streptococci grow poorly in urine, while indifferent streptococci grow abundantly. Hemolytic streptococci live longer in a medium composed of the inorganic salts of urine alone than in one in which the normal amount of urea is added to the

saline constituents. The nondialyzable constituents of urine are not suitable for the support of growth of the hemolytic variety, but suffice for the growth of the indifferent organisms for a considerable time.

AUTHORS' SUMMARY.

EFFECT OF IODINE ON THE TUBERCLE BACILLUS AND EXPERIMENTAL TUBERCULOSIS. G. KNAYSI, J. Infect. Dis. **50**:255 and 261, 1932.

The results of the present experiments show that iodine is toxic to the tubercle bacillus cells, for these cells were unable to grow on slants after thirty minutes' contact with as high a dilution of iodine as 1 : 10, or to infect guinea-pigs after an exposure of fifteen minutes to iodine in the dilution $1 : 5 \times 10$. My results are contrary to the report of DeWitt and Sherman that compound solution of iodine is not able consistently to kill the tubercle bacillus cells even after an exposure of twenty-four hours. The results obtained by these investigators become understandable if one remembers that they used cell clumps in their test tube experiments and dried cells in their experiments on animals. When a clump of cells is placed in an iodine solution, the iodine reacts with the lipoids of the cells on the outside, and this slows down its diffusion to the interior of the clump. On the other hand, it is a fact that the cells become less permeable on drying. For instance, they stain less readily, and it becomes difficult to demonstrate satisfactorily in dried cells intracellular substances such as fat and glycogen without a relatively long application of the reagent. The effects of clumping and drying may be put in evidence by studying the diffusion velocity of iodine in strips of filter paper, wet and dry, and with and without previous imbibition of an emulsion of lecithin. It will be found that iodine diffuses most slowly in a strip of filter paper that has been immersed in an emulsion of lecithin and allowed to dry, less slowly if the lecithin-treated paper has not been dried, faster in a dry, untreated strip, and fastest in a strip wet with distilled water.

Iodine may be injected intravenously into the body of the rabbit over relatively long periods of time without apparent harm to the health of the animal or injury to the thyroid gland. The dose used in most of these experiments was 2 mg. per kilogram of body weight, administered twice a week over a period of about two months, from an aqueous solution containing three times as much of potassium iodide. The results show that such a small dose is not effective in the treatment of tuberculosis, probably because it is quickly neutralized by the alkali reserve of the blood. A dose of 30 mg. of iodine per kilogram of body weight does not kill a normal animal, but one of 20 mg. per kilogram is fatal to a rabbit with severe miliary tuberculosis. This subject deserves further consideration under more appropriate conditions.

AUTHOR'S SUMMARIES.

THE INFLUENCE OF BLOOD AND OF EXUDATE ON THE COLON BACTERIOPHAGE. M. APPLEBAUM and W. J. MACNEAL, J. Infect. Dis. **50**:269, 1932.

Purulent exudate, even when diluted, exerts an interfering influence on the lytic action of bacteriophage against the colon bacillus, provided that the colon bacillus is capable of active growth in the medium employed. Human blood serum and rabbit blood serum exert a similar but less powerful interfering influence, which becomes evident when pathogenic strains of the colon bacillus recently obtained from human infections are employed. Whole blood produces an effect similar to that of serum. Suspensions of erythrocytes in an indifferent medium seem to exert little, if any, influence on the bacteriophage phenomenon in relation to the colon bacillus. These observations have a bearing on the use of bacteriophage in the treatment of infectious disease.

AUTHORS' SUMMARY.

PURIFICATION OF THE VIRUS OF VACCINIA. C. A. BEHRENS and L. B. MORGAN, J. Infect. Dis. **50**:277, 1932.

Two methods, (a) the iso-electric and (b) the aluminum gel, have been developed for the purification of the virus of vaccinia. The iso-electric and the

aluminum gel methods are both satisfactory for neurovirus emulsions, but only the aluminum gel method is applicable to the dermovirus emulsion.

AUTHORS' SUMMARY.

BLOOD CULTURE IN RHEUMATIC FEVER. L. E. COOLEY, J. Infect. Dis. **50**:330, 1932.

Blood cultures from twenty-five children with rheumatic fever remained sterile for one month, except for an occasional contaminant. The positive results obtained by others were not confirmed.

AUTHOR'S SUMMARY.

RAT-BITE FEVER ASSOCIATED WITH SPOROTHRIX. N. P. ANDERSON and B. K. SPECTOR, J. Infect. Dis. **50**: 344, 1932.

A typical case of rat-bite fever is reported, the evidence indicating that a sporothrix-like organism played a part in the attack. As far as we know, this is the first time that such an organism has been isolated from a patient suffering from rat-bite fever.

AUTHORS' SUMMARY.

DISSOCIATION IN STREPTOCOCCUS SCARLATINAE. E. DELVES, J. Infect. Dis. **50**: 350, 1932.

The streptococcus of scarlet fever was dissociated into three main colonial types, S, SR and R. The S colonies were small, smooth and conical, grew diffusely in broth and were opsonically specific. The SR colonies were granular on the surface, with an even but irregular outline, and grew in broth with some sedimentation, although the supernatant medium was slightly cloudy. The R colonies were rough-surfaced, with fimbriated margins, and gave a clumpy growth in broth, the supernatant medium remaining clear. Neither the SR nor the R colonies were opsonically specific, but reverted strains regained this specificity. The S culture when stained was composed of short chains of small cocci. The stained SR chains were of medium length and composed of large cocci, while the R cultures showed long chains of large cocci with flattened opposing surfaces. The Gram reaction became more variable as the dissociation proceeded from S to SR to R. The virulence tests, while the results were not clearcut, owing to the fact that streptococci lose virulence on an artificial medium, would indicate that S was more virulent than R. Reversion in the animal body to forms that were able to cause abscesses, as well as reversion by serial transplants in an artificial medium, was observed. Dissociation of S to SR to R was also noted in infusion immune serum broth of p_H 7.8, while neutral broth was not as effective.

AUTHOR'S SUMMARY.

DISSOCIATION OF STREPTOCOCCI. L. E. COOLEY, J. Infect. Dis. **50**:358, 1932.

Six different strains of streptococci associated with rheumatic fever and arthritis were grown on cholocate agar for several months. Five of the strains showed definite evidences of spontaneous dissociation, two strains dissociating to the R form, while three remained as the SR form. In young colonies of one of the R forms, definite bacilli were seen. These bacilli later divided to form the adult irregular coccoid forms. The other R form showed no bacillary types during its growth. Coccobacilli and short, thick bacilli were seen in two of the SR forms during their period of growth. One of the R forms was more virulent for mice than the S form of the same strain. There was no difference in virulence for mice between the S, SR or R forms of the other strains. All of the dissociated strains were repeatedly brought back to the original S form by being grown in dextrose broth medium.

AUTHOR'S SUMMARY.

EXPERIMENTS ON A FILTRABLE PHASE IN THE LIFE HISTORY OF THE TUBERCLE BACILLUS. R. R. MELLON, Tubercle **13**:10, 1931.

Employing filtrates of tuberculous material from sixteen different sources, Mellon reports that in two of thirty-seven animals classic tuberculosis resulted, and that the typical Koch bacillus was recovered in pure culture. These positive results were obtained only when the original material was richly seeded with the granular form of the tubercle bacillus. Histologic evidence of tubercles in guinea-pigs is not of itself sufficient proof of filtrability, since such lesions can be caused by gram-negative paratyphoid-like micro-organisms. The relation of this group of micro-organisms to lesions indistinguishable from the necrobiotic type of tubercles in guinea-pigs must always be kept in mind. H. J. CORPER.

THE ETIOLOGY AND PATHOGENESIS OF LYMPHOGRANULOMATOSIS. TITU VASILIU, Ann. d'anat. path. **8**:815, 1931.

From a review of the literature and from personal studies, Vasiliu concludes that tuberculosis is often mixed with lymphogranulomatosis, at times conspicuously, but at other times so intimately that one can hardly detect its presence on microscopic examination. Animals susceptible to tuberculosis become tuberculous in a high number of instances when inoculated with lymphogranulomatous material whether an infection with acid-fast bacilli was or was not found in the latter.

On the other hand, in a number of instances, lymphogranulomatosis associated with tuberculosis produces no lesions (in the rabbit and guinea-pig) of the customary tuberculous type. Nevertheless, tissues from animals thus infected yield cultures of Koch's bacilli on inoculation in artificial mediums. Again, cases were reported in which tissues showing no acid-fast micro-organisms produced tuberculosis in animals on reinoculation.

Lesions closely resembling those of lymphogranulomatosis were produced with lymphogranulomatous material, particularly with that associated with tuberculosis.

Filtrates obtained from tubercle bacilli have sometimes caused lesions resembling very much those of lymphogranulomatosis. Tubercle bacilli have very rarely caused such lesions.

Although Vasiliu is of the opinion that the etiology of lymphogranulomatosis is not established, he does consider that the relationship between the tubercle bacillus and lymphogranulomatosis is not entirely eliminated. B. M. FRIED.

SECONDARY BRONCHOGENIC ECHINOCOCCIC CYSTS OF THE LUNG. F. DÉVÉ, Ann. d'anat. path. **9**:77, 1931.

Most uncomplicated hydatid cysts of the lung are fertile when they rupture, and in addition to the daughter cysts, innumerable scolices are dispersed throughout the bronchial tree. Contrary to the opinion of certain authors, these scolices are capable of producing secondary cysts as Dévé demonstrated experimentally in 1904. The experiments have been repeated, and a series of photomicrographs shows the various steps in the dissemination, encystment and growth of the scolices. In the literature, five cases of multiple echinococcic cysts are described, which can be explained as due to secondary implants following rupture of a primary cyst into a bronchus. ALBERT F. DE GROAT.

RABIES. P. REMLINGER and J. BAILLY, Ann. Inst. Pasteur **47**:608, 1931.

The article, apparently the first of a series, presents various phases of the activity of the virus. The virus was often demonstrated in the spleens of various infected animals, most frequently in those of cats (seven of fifteen animals). Liver and kidney also yielded the virus. Certain areas in the nervous system were occasionally encountered in which there was no virus. A study of five fixed viruses confirmed the idea that these vary in virulence and in symptoms produced. Frogs and toads were found to be completely refractory. "The passage of fixed virus

into the central nervous system of vaccinated animals is no more a question of strain than of the method of treatment or of the animal used." Dilution was found not to attenuate the virus. A review of four cases in which repeated vaccination was practiced (in one, four times in four years) indicated that no untoward reactions should be expected.

M. S. MARSHALL.

SUBACUTE INGUINAL LYMPHOGRANULOMATOSIS. C. LEVADITI, P. RAVAUT, P. LÉPINE and R. SCHOEN, Ann. Inst. Pasteur **48**:27, 1932.

The disease appears to be due to a specific virus, "the lymphogranulomatous virus," present in the inguinal glands during this disease, which, on intracerebral injection into monkeys induces typical inflammatory changes in the meninges, paralysis and, on some occasions, death. The virus was not found other than in cases of this disease. The most virulent of strains isolated was, after twelve passages through monkeys, still virulent for man (used in a case of dementia paralytica). The virus is filtrable, loses its pathogenicity after heating at 60 C. for thirty minutes, is stable in glycerin, does not resist drying, resists antiseptics well, except formaldehyde 1 : 1,000, and carries a negative charge. Monkeys and mice were successfully inoculated; rabbits, rats and cats were not susceptible. Silent infections and other variations in virulence were noted. The histologic picture was characterized by infiltration of the meninges, extensive perivascular lymphoma, morphologic integrity of nerve cells and necrotic areas in human ganglions. Photographs and colored plates of these changes are given. Inoculation in the inguinal nodes induced bilateral inguinal adenitis, from which the virus was recovered ten weeks after inoculation. Inoculation of the prepuce was also followed by adenitis, a tendency to ulceration followed by spontaneous resorption, inguinal and axillary polyadenitis and tumefaction. The affinity for the nervous system is less marked than that of some other viruses. The infection is generalized, since liver, kidney, spleen and bone marrow yielded the virus, although blood inoculations failed. Monkeys surviving intraganglionic inoculation are refractory to intracerebral inoculation, and serum from patients with the disease neutralized the virus in vitro, although vaccination proved difficult.

M. S. MARSHALL.

TUBERCULOUS ULTRAVIRUS. G. SANARELLI and A. ALESSANDRINI, Ann. Inst. Pasteur **48**:144, 1932.

The ultravirus in collodion sacs introduced into the peritoneal cavity of the guinea-pig induced death due to "tuberculosis of the Calmette-Valtis type"—adenitis, slight enlargement of the spleen, acid-fast elements, but no tubercles. Two or three serial transfers through guinea-pigs resulted in typical experimental tuberculosis, with tubercles and acid-fast rods. Tubercle bacilli in collodion sacs implanted in the animal induced only the picture of an infection with the ultravirus. Prolonged exposure, or infection, still gave the same anatomic changes, without tubercles. The acid-fast elements derived from infected guinea-pigs showed attenuated pathogenicity. The ultravirus exhibited lymphotropic properties—an affinity for lymph nodes and serous cavities—with proliferative inflammatory processes, hyperplastic or caseogenous, and giant cells, but no tubercles. On the second animal transfer, the spleen usually showed a few nodules; subsequent transfers resulted in increasing dissemination. Cultivation of tubercle bacilli from the infected animal is difficult, even in early animal passage in which bacillary forms appear. Colonies appear only after prolonged incubation, in keeping with the conception of poor vital energy on the part of ultravirus granules.

FROM THE AUTHORS' CONCLUSIONS.

EXPERIMENTAL TRACHOMA. UGO LUMBROSO, Arch. Inst. Pasteur de Tunis **20**:253, 1931.

After reviewing the conflicting reports with regard to the rôle of Bacterium granulosis in trachoma, Lombroso proceeds to discuss further experimental work

in which he used his types A, B and C, bacteriologically described in a previous article in the same periodical. Granulation was produced in one of four species of monkeys tested with A, indicating a refractory state on the part of the common Macacus cynomolgus and other species. Apparent infection with type B was indicated in several species of monkeys; a failure was attributed to the strain of culture used. When M. cynomolgus only was used, natural granulation of the conjunctiva was noted in animals inoculated with true type C, but the strains were considered avirulent. Representative type strains were injected into two series of human subjects (seven in all), with results that indicated, as in the experiments on animals, that type A is rarely pathogenic, that type B is particularly virulent, and that type C never induces infection.

M. S. MARSHALL.

SILENT INFECTION OF MAN BY THE VIRUS OF DISTEMPER. CHARLES NICOLLE, Arch. Inst. Pasteur de Tunis **20**:321, 1931.

The question why there are a number of infections transmitted from animal to man, but none from man to animal, is raised. The virus of distemper was injected subcutaneously into a man and into a monkey. Although of proved virulence, it caused no symptoms, but the blood of the human subject reinjected into rigidly quarantined dogs induced the infection. Nicolle reasons that man is susceptible to infection with the virus in the *forme inapparente;* that man may thus act as a reservoir for some diseases of animals, although the fact is not recognized, and that when two species are susceptible to a virus, one typically and the other without apparent symptoms, the disease is older in the second species.

M. S. MARSHALL.

MEXICAN TYPHUS. CHARLES NICOLLE, Arch. Inst. Pasteur de Tunis **20**:324, 1931.

Nicolle is unequivocal in stating that Mexican typhus and the European disease are the same. Clinical differences are secondary: more extensive eruption, less significant cerebral and cardiac symptoms, less severe disease even in immigrants, with more rapid convalescence, and a much greater tendency to develop hemorrhages, especially epistaxis. The viruses of Europe and Mexico are identical on cross-protection tests. In the guinea-pig, the Mexican virus induces an earlier fever of shorter duration and orchitis, which is not produced by the Tunisian virus. The latter shows a cerebral localization. The white rat and gray rat have a silent infection with the Tunisian virus; in Mexico the black rat was found to act as a reservoir of the infectious agent. The systematic relationship between Mexican typhus, the typhus of valleys of the Andes and European typhus is briefly considered.

M. S. MARSHALL.

BACILLUS PROTEUS AND TYPHUS. F. LECHUITON, Arch. Inst. Pasteur de Tunis **20**:444, 1932.

Bacteriophage-lysed filtrates of B. proteus X 19 failed to induce typhus in guinea-pigs, nor did they produce immunity to typhus. Similar results obtained with formaldehydized filtrates and also with strains placed in contact with the brain tissue of animals with typhus under a variety of conditions. Strains that had lost the property of agglutinability did not recover it when in contact with the brain tissue of infected guinea-pigs or with the blood of infected monkeys.

FROM AUTHOR'S CONCLUSIONS.

GLANDERS IN A WOMAN. W. A. AFANASSJEW, Centralbl. f. allg. Path. u. path. Anat. **53**:148, 1931.

Glanders, apparently starting in the nose, in a 50 year old peasant woman resulted in the production of pea-sized nodules in the skin of the nose and face,

right lung and spleen. The nodules were exudative rather than neoplastic. In the sublobular veins of the liver were emboli of liver cells.

GEORGE RUKSTINAT.

ACUTE SEPTIC AVIAN TUBERCULOSIS IN A MAN. H. NASSE, Centralbl. f. allg. Path. u. path. Anat. **53**:209, 1931.

The body of a 53 year old metal-worker was entirely covered with a finely speckled, red-brown exanthem; each lung had about fifty pinhead-sized yellow nodules just beneath the pleura; nodules varying in size from that of a millet seed to that of a hazelnut were found in the liver, spleen, epiglottis, bowel and kidney, and hazelnut-sized caseous masses were found in the tracheobronchial lymph glands. The nodules contained clumps of tubercle bacilli, nuclear débris at their centers and many monocytes. Lymphocytes and polymorphonuclear leukocytes predominated; epithelioid cells were scarce and giant cells entirely absent. Coupled with the histologic picture in these nodules, which was typical of avian tubercles, was a history that the deceased person had eaten many raw eggs. Nasse cites the startling estimate that 11 per cent of chickens in Germany are tuberculous, and that from 3 to 7 per cent of eggs on the market contain tubercle bacilli.

GEORGE RUKSTINAT.

TUBERCLE BACILLEMIA IN TUBERCULOSIS OF THE SKIN. F. KOCH, Deutsche med. Wchnschr. **58**:90, 1932.

With Löwenstein's culture method for detecting tubercle bacilli in the blood, Koch failed to obtain any positive results in twelve cases of lupus vulgaris, two of annular granuloma, two of indurated erythema, four of lupus erythematosus, four of verrucous tuberculosis of the skin and one of tuberculous epididymitis. He cannot offer any explanation why his results should differ so widely from those obtained by Löwenstein.

ENTEROCOCCUS ENDOCARDITIS. GERHARD ROSENBERG, Klin. Wchnschr. **11**:359, 1932.

The clinical progress and the results of a postmortem examination in a case of aortic and mitral endocarditis in which the infecting organism was an enterococcus of type B are reported. The duration of the infection was ten weeks. There were embolic mycotic abscesses and perivascular scars of the myocardium, and infarcts of the spleen. The abscesses differ from the lesions of endocarditis lenta (Schottmüller), caused by Streptococcus viridans. EDWIN F. HIRSCH.

SEPSIS DUE TO BACILLUS INFLUENZAE. F. E. KOCH, München. med. Wchnschr. **79**:706, 1932.

In a girl, aged 3½ years, with sepsis caused by B. influenzae and a diphtheroid infection of the throat, there were found after death bilateral confluent bronchopneumonia, pleuritis, fatty changes of the heart and liver, and marked edema of the brain. The blood gave a pure growth of B. influenzae.

EDWIN F. HIRSCH.

TAPEWORM OF THE HUMAN GALLBLADDER. E. OPFER, Virchows Arch. f. path. Anat. **279**:193, 1930.

Opfer says that his is the third recorded case of tapeworm infestation of the human gallbladder. The patient was a woman, aged 52, who died rather suddenly with symptoms of acute gallbladder disease. Necropsy revealed acute generalized purulent peritonitis, which was secondary to ulcerative and phlegmonous cholecystitis with partial necrosis of the wall. The gallbladder was filled with purulent bile, which contained a tapeworm (Taenia saginata) 25 cm. long. There were no calculi.

W. SAPHIR.

FILTRATES OF CULTURES OF STAPHYLOCOCCI. HANS GROSS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **73**:14, 1931.

The hemolyzing, necrotizing, leukocidal and toxic properties of filtrates of certain cultures of staphylococci are manifestations of the same antigenic substance. They are all present in potent filtrates, show identical thermoresistance and are all absorbed by antiserums. The substance promoting clotting which is found in some filtrates differs qualitatively from those previously mentioned.

I. DAVIDSOHN.

THE VIRUS OF LYMPHOGRANULOMA INGUINALE. S. HELLERSTRÖM and E. WASSÉN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **73**:110 and 114, 1931.

Intraperitoneal injection of this virus produced peritonitis with a characteristic cellular exudate. The latter contained the virus, which was also demonstrated in the blood and in the spleen. The virus passed through the scarified skin of monkeys and infected them without producing a local reaction. The virus passed Berkefeld and Chamberland filters, was quickly destroyed by glycerin (p_H 5) and resisted freezing for at least twenty-two days.

I. DAVIDSOHN.

A NEW STRAIN OF CHICKEN LEUKOSIS. J. ENGELBRETH-HOLM, Ztschr. f. Immunitätsforsch. u. exper. Therap. **73**:126, 1931.

Leukosis found in a Plymouth Rock chicken was transmitted for ten generations. Blood and suspensions of organs were used successfully for intravenous, intramuscular and subcutaneous injections. Attempts at alimentary transmission did not succeed. The period of incubation was shortened and the frequency of "takes" increased with repeated passages. The opinion of Furth is confirmed that lymphatic leukosis in chickens is a nontransmissible disease *sui generis*, occurring spontaneously and not related to myeloid and erythroleukotic forms.

I. DAVIDSOHN,

THE INFECTIOUSNESS OF PERSPIRATION IN SYPHILIS. IMMO KÖHNE, Ztschr. f. Immunitätsforsch. u. exper. Therap. **73**:279, 1932.

Rabbits that received injections of the perspiration of syphilitic patients did not become infected. No infection resulted when the testicles and popliteal lymph nodes of these rabbits were injected into a second group of rabbits. No spirochetes were detected in the perspiration in the dark field. When spirochetes were added to the perspiration, the mixture produced an infection in the rabbit, although the motility of the spirochetes was quickly inhibited after the addition of the perspiration.

I. DAVIDSOHN.

THE NATURE OF THE BACTERIOPHAGE. Z. W. JERMOLJEWA, I. S. BUJANOWSKAJA and W. A. SEVERIN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **73**:360, 1932.

Chemical analysis of filtered bacteriophage revealed that it is not a protein or a nucleoproteid, and that it consists of particles smaller than those of albumin. The nonprotein nature was confirmed by means of cataphoresis. It could be produced from dead bacterial bodies. It is concluded that the nature of bacteriophage is not that of a living substance.

I. DAVIDSOHN.

Immunology

ANTIGENIC RELATIONSHIP OF SHIGELLA DISPAR. H. WELCH and F. L. MICKLE, J. Infect. Dis. **50**:524, 1932.

A Flexner diagnostic serum contains an agglutinin for the dispar type, the titer of which is at least 50 per cent of the titer of the major agglutinins. It is

demonstrated by agglutination and agglutinin absorption that the organisms responsible for dispar agglutinins in the Flexner diagnostic serum are the Strong 2 (Army Medical Museum) and Flexner 6 (Army Medical Museum) strains. Eight of the fifty-three strains studied were capable of absorbing dispar agglutinins from Flexner diagnostic serum. Emphasis is placed on the diagnostic value of recognizing the dispar antigenic component of the Flexner 6, the Strong 2 and particularly the V strain used as stock Flexner in European laboratories. It is suggested, in spite of the discrepancies in fermentative reactions, that neither the dispar nor the Sonne types should be excluded from the Flexner series until further work is brought forward to substantiate the value of such a procedure.

AUTHORS' SUMMARY.

AGGLUTININ-ABSORPTION STUDIES ON BRUCELLA. W. N. PLASTRIDGE and J. G. MCALPINE, J. Infect. Dis. **50**:555, 1932.

Agglutinin-absorption data obtained on 142 strains of Brucella of human, bovine, porcine, caprine and equine origin are presented. A comparison of the identifications of these strains by their ability to utilize dextrose and their behavior on Huddleson's dye plates with their serologic identifications shows that the agglutinin-absorption test failed to differentiate between Br. abortus and Br. melitensis so far as twenty-three, or 15 per cent, of the strains studied were concerned. In general, the results obtained confirm the opinion expressed by Burnet, namely, that while it is possible to classify some strains of Br. melitensis as such by means of the agglutinin-absorption test, it is impossible to identify strains of Br. abortus by means of this test with any degree of certainty. Evidence of variation in the serologic properties of the members of the genus Brucella, especially Br. melitensis, under ordinary laboratory conditions has been noted and discussed from the standpoint of explaining the lack of agreement in the results reported by various investigators.

AUTHORS' SUMMARY.

SKIN REACTIONS TO NECATOR AMERICANUS IN PERSONS INFECTED WITH THE COMMON INTESTINAL PARASITES. G. W. BACHMAN and R. RODRIGUEZ-MOLINA, Porto Rico J. Pub. Health & Trop. Med. **7**:287, 1932.

For practical application of the intracutaneous test in detecting the presence of Necator americanus in persons infected with two or more intestinal nematodes, the measurable characteristics are too variable, and the reactions are not significantly specific.

FROM AUTHORS' SUMMARY.

CROSS-IMMUNITY BETWEEN SOUTH AFRICAN TYPHUS AND TICK-BITE FEVER. ADRIANUS PIJPER and HELEN DAU, Brit. J. Exper. Path. **13**:33, 1932.

The virus of South African typhus confers immunity in guinea-pigs against the virus of tick-bite fever. The virus of tick-bite fever, however, does not confer immunity in guinea-pigs against South African typhus.

AUTHORS' SUMMARY.

THE SEROLOGICAL DIAGNOSIS OF TYPHOID AND PARATYPHOID FEVERS. J. SMITH, J. Hyg. **32**:143, 1932.

An analysis of the results of serologic study of blood specimens submitted during the past two years for the Widal test has been made. The serums from persons with typhoid and paratyphoid fever were examined in particular for their content of agglutinin for the H and O antigenic constituents of Bacillus typhosus and Bacillus paratyphosus B. The results indicate that, from the point of view of early diagnosis it is essential to use the O-antigen of B. typhosus, but that no particular advantage is derived from the use of the O-antigen of B. paratyphosus. A comparison of the value of suitable living and killed antigens has been made. The two types of antigen appear to be equally effective, but for convenience and

stability the suspensions issued by the Standards Laboratory, Oxford, have proved entirely satisfactory. Cases showing the serologic difficulties that arise when a mixed specific and nonspecific form of the H-antigen of B. paratyphosus B is used are described.

AUTHOR'S SUMMARY.

ANTICOMPLEMENTARY SERA. R. D. MACKENZIE and R. S. MARSHALL, J. Path. & Bact. **35**:175, 1932.

An anticomplementary action has been noted in the serums of natives of Northern Nigeria. This action is present in the serums of almost all the persons with sleeping sickness whom we have examined, and to a lesser degree in the serums of those suffering from other conditions. It is thermostable and cannot be removed by filtration. It has no relation to the amount of natural complement present in the serum. Its significance is not understood. It is strong enough to interfere with the carrying out of complement-fixation tests by the usual methods.

AUTHORS' SUMMARY.

Tumors

GANGLIONEUROMA. J. A. BIGLER and A. HOYNE, Am. J. Dis. Child. **43**:1552, 1932.

Ganglioneuromas are rarely reported in children. The diagnosis is difficult, as the symptoms are usually due to pressure on adjacent tissues or organs. Two cases are reported: In one, a mediastinal ganglioma caused compression and displacement of the trachea, with laryngeal or tracheal obstruction. In the other, a ganglioma at the upper pole of the right kidney was discovered at necropsy. Microscopically, these tumors were true benign ganglioneuromas. Following a review of the literature a classification of the reported cases is outlined on the basis of the schematic diagram of the development of the sympathetic nervous system by Landau and modified by Schultz. Three main types of tumors develop from the formative cells of the sympathetic nervous system: neuroblastomas from neuroblasts, chromaffinomas or paraganglionomas from the pheochromoblasts and ganglioneuromas from the adult ganglion cells. Intermediate or mixed types may occur. The neuroblastoma, which is the most common type in children, arises frequently in the suprarenals, resembles a small cell sarcoma, and metastasizes early to the lymph nodes, the bones and the liver. The rare chromaffinoma is small and seems to be benign. The ganglioneuroma is considered ripe and benign when early formative cells are not present. The ripe ganglioneuroma is rare in children; it grossly resembles a fibromyoma but microscopically possesses a characteristic appearance. Ganglioneuromas which contain early formative cells may ripen and become benign or may metastasize.

RALPH FULLER.

ALEUKEMIC, MYELOGENOUS CHLOROMA. LEONARD A. SWANSON, Am. J. Dis. Child. **44**:140, 1932.

A case of chloroma occurring in a girl, 2 years of age, and terminating in death within sixty-eight days after the onset of symptoms has been described. Profound anemia was present when the patient was first examined, twenty-three days after the onset of symptoms, and progressed in severity to the time of death. Roentgenograms of the long bones taken a month after the onset of the disease did not indicate a generalized involvement of the bone marrow. Repeated examination of the blood failed to disclose any leukemic changes. The tumor was primary in the bones of the skull, with the early production of exophthalmos, and metastases were present in the lymph nodes, ovaries and suprarenals. Both the primary and the secondary tumors gave a strongly positive reaction to oxydase. The characteristic green color was obscured in the primary tumors by necrosis and hemorrhage, but was typical in the metastases. Roentgen therapy was instituted within a month after the onset of symptoms, with no beneficial effects.

AUTHOR'S SUMMARY.

MULTIPLE EPITHELIOMAS ORIGINATING FROM CONGENITAL PIGMENTED NEVI. R. NOMLAND, Arch. Dermat. & Syph. **25**:1002, 1932.

A case, apparently unique in the literature, is described in which epitheliomas arose in adult life from pigmented basal cell nevi present since birth. The patient was a woman 38 years old.

HISTOLOGIC CLASSIFICATION OF TUMORS OF THE CENTRAL NERVOUS SYSTEM. G. ROUSSY and C. OBERLING, Arch. Neurol. & Psychiat. **27**:1281, 1932.

On the basis of studies of 251 cases, Roussy and Oberling offer a simplified classification of cerebral tumors into five main types: glioma (arising from neuroglia), ependymochoroid neoplasms (arising from the ependymal lining including that of the choroid plexus), ganglioneuroma (arising from the ganglion cells), neurospongioma (originating from neuroblasts and spongioblasts) and neuroepithelioma. Each group is subdivided; for instance, glioma is subdivided into astrocytoma, oligodendrocytoma and other types of tumor. Of the 251 tumors studied, 178 were gliomas, 26 ependymomas and the rest neurospongiomas, ganglioneuromas and unclassified tumors.

GEORGE B. HASSIN.

HISTOLOGIC DIAGNOSIS OF TUMORS OF THE BRAIN. PERCIVAL BAILEY, Arch. Neurol. & Psychiat. **27**:1290, 1932.

Bailey recognizes three great families of primary tumors of the brain: medulloblastoma, multiform glioblastoma and astrocytoma. They differ in age of onset, site of origin and biologic behavior. Medulloblastoma, for instance, is almost exclusively a cerebellar tumor in children. Glioblastoma, also described as multiform spongioblastoma, occurs almost exclusively in adults, in the cerebral hemispheres, while astrocytoma is the classic glioma, a slowly growing tumor. Groups less frequently observed are comprised of oligodendroglioma (relatively benign), unipolar and bipolar spongioblastoma, especially the type that grows in the vicinity of the optic chiasm, astroblastoma, ependymoma and pinealoma, ganglioneuroma and neuro-epithelioma. Bailey states that perhaps 12 or 15 per cent of the gliomas cannot be affiliated with any of the foregoing groups, and that the classification is not only of academic, but also of practical importance.

GEORGE B. HASSIN.

TUMORS OF THE SHEATHS OF THE NERVOUS SYSTEM. WILDER PENFIELD, Arch. Neurol. & Psychiat. **27**:1298, 1932.

The primary tumors of the meninges are classified by Penfield as meningeal fibroblastoma, otherwise known as dural endothelioma, meningioma and psammoma; meningeal sarcoma, melanoblastoma, lipoma and other types. To tumors of the nerve sheaths the author refers perineurial fibroblastoma, otherwise known as neurinoma, and peripheral glioma which the author proposes to call schwannoma, for, he thinks, they originate from the Schwann cells or their precursors.

GEORGE B. HASSIN.

INTRACRANIAL CHORDOMA. HERMAN SELINSKY, Arch. Neurol. & Psychiat. **28**:413, 1932.

Chordoma in the region of the pituitary body produces the usual signs and symptoms of increased intracranial pressure, but no manifestations of dispituitarism. This feature was noted in Selinsky's patient, who complained of progressively failing vision and various ocular disturbances (hemianopsia and palsies of various optic muscles). Necropsy revealed a chordoma, the size of a plum, over the sella, which was destroyed.

GEORGE B. HASSIN.

AN OSTEOBLASTIC OSTEOID TISSUE-FORMING TUMOR OF A METACARPAL BONE. HENRY L. JAFFE and LEO MAYER, Arch. Surg. **24**:550, 1932.

A tumor of the fourth metacarpal bone was described. It began when the patient, a girl, was 12 years of age. After growing slowly for almost three years, it began to grow rapidly. The tumor mass was removed; it measured 10 by 6.5 by 6 cm. Only the articular head of the metacarpal bone remained. The tumor was of such consistency that it could be cut with a knife, but it was granular and firm. Histologically, it showed a marked production of osteoid tissue and also the formation of trabeculae of normal, newly formed bone. The osteoid tissue arose from cells that had many of the features of osteoblasts. The tumor has not recurred two years after operation, although on casual examination the histologic appearance suggests the diagnosis of osteogenic sarcoma. It is believed that this tumor is an osteoblastic, osteoid-forming tumor of slow growth, and that the prognosis is favorable. Early in the course of the growth a biopsy was made. The histologic pictures of the biopsy specimen and the surgically removed specimen are practically identical.

The only other report in which tumors of similar nature have been described is that of Bergstrand under the title of "Ueber eine eigenartige, wahrscheinlich bisher nicht beschriebene osteoblastische Krankheit in den langen Knochen der Hand und des Fusses" (*Acta radiol.* **11**:597, 1930). H. L. JAFFE.

SOME FEATURES OF GLIOBLASTOMA MULTIFORME. E. M. DEERY, Bull. Neurol. Inst., New York **2**:157, 1932.

The overgrowth of vascular elements found in glioblastoma multiforme has been studied at necropsy in a series of ten cases. Some vessels showed an overgrowth strictly limited to the endothelial cells. Other vessels presented an unaltered intima, but the adventitial elements had undergone hyperplasia. Less frequently, a combination of both endothelial and adventitial overgrowth was found to occur in the same blood vessel. These vascular reactions are not strictly specific, as they may be found in a lesser degree in other conditions, including other types of tumor. The distribution, type and degree of hyperplasia of the vascular elements vary greatly, and large areas in every tumor may contain only normal vessels. In the endothelial form of overgrowth the endothelial cells themselves appear to elaborate the heavy reticulin-collagen framework which is characteristic of this type of reaction. Necrosis, so common in glioblastoma multiforme, is probably caused as much by focal toxic factors as it is by the decrease in blood supply. Large numbers of phagocytic cells are produced by the adventitial tissues of the vessels bordering an area of necrosis. The majority of these phagocytes eventually become indistinguishable from the gitter cells of microglia.

AUTHOR'S SUMMARY.

THE BLOOD SUPPLY OF THE GLIOMAS. C. A. ELSBERG and C. C. HARE, Bull. Neurol. Inst., New York **2**:210, 1932.

In the gliomas of the brain there is a close connection between the distribution of the blood vessels and the manner in which they infiltrate the brain tissue. On gross and microscopic postmortem examination, the differences between the number of blood vessels in the central and the peripheral parts of the tumors and the number of those in the adjacent brain tissue are striking. In the astrocytomas and the medulloblastomas, the largest number of vessels occur in the central part of the growths, and there is no increase in the number of arteries in the adjacent white matter. In the glioblastoma multiforme, the peripheral areas of the neoplasm contain the largest number of arteries, and the vessels in the adjacent tissue of the brain are more numerous than in normal white matter or in the part of the brain which is adjacent to the margins of the astrocytomas and the medulloblastomas. As there is a close connection between blood supply and active growth, it has been possible to gain some insight into the manner in which the astrocytomas,

medulloblastomas and glioblastomas increase in size and infiltrate the brain which surrounds them. The glioblastoma multiforme is a rapidly growing and malignant tumor, and in the final analysis, the "active" infiltration of the brain and the peripheral type of growth are due to its malignancy, which is the major factor. The differences in blood supply and in the manner in which the brain is invaded in the astrocytoma and the medulloblastoma, on the one hand, and in the glioblastoma multiforme, on the other, are expressions of the varying degrees of malignancy. The difference in the situation of the blood vessels between the astrocytoma and medulloblastoma and the glioblastoma multiforme can be recognized at operation, and this has led us to modify and to alter to some extent the technic used for the removal of such growths. In order to gain an approximate idea of the vascularity of different parts of the growth and of its size, the suggestion is made that at operation the tumor should be bisected before an attempt to remove it is made. This procedure will permit the surgeon to orient himself better regarding the size and removability of the growth. If he is dealing with an astrocytoma or a medulloblastoma, the central, most actively growing part should be removed first. The excision of the peripheral parts may be simplified by this technic. In the glioblastoma multiforme, on the other hand, the periphery of the tumor should be removed with especial care. AUTHORS' SUMMARY.

VENOUS AND ARTERIOVENOUS ANGIOMAS OF THE BRAIN. S. BROCK and C. G. DYKE, Bull. Neurol. Inst., New York **2**:247, 1932.

Eight instances of intracranial angioma are described. In four, extracranial vascular lesions coexisted. An unusual instance of venous angioma of the retina, chiasm, midbrain and cerebellum is described. The important optic signs were homonymous hemianopia and unilateral exophthalmos. In the arteriovenous variety the cardiovascular phenomena were of diagnostic significance. They included enlargement of the intracranial, cranial, extracranial and carotid arteries and of the heart; a systolic mitral murmur and a mild degree of tachycardia. A low systolic pressure with a much reduced diastolic blood pressure and a Corrigan pulse were sometimes found. The resemblance of the cardiovascular disturbances to those seen in aortic regurgitation is commented on. An arterial bruit of extracranial or of intracranial origin is an important sign, too often overlooked. The significant roentgenographic observations consisted of intracerebral calcifications, and dilatation and tortuosity of the vascular grooves in the bones of the skull. The peculiar character of the calcification found in the venous angiomas was pathognomonic. AUTHORS' SUMMARY.

PROPERTIES OF THE CAUSATIVE AGENT OF A CHICKEN TUMOR. J. B. MURPHY and E. STURM, J. Exper. Med. **56**:483, 1932.

Water extracts of desiccates of certain relatively slow-growing strains of chicken tumors I and X, or the exudates from such tumors, definitely inhibited the growth of a mouse sarcoma and were without effect on a mouse carcinoma or mouse tumor S/37, a rapidly growing sarcoma derived from the stroma of a carcinoma. Extensive control tests with extracts from rapidly growing chicken tumors, and from tissues of normal and immune chickens showed no inhibiting action. There was no demonstrable action on the mouse tumors of serums from immunized rabbits, which neutralize the chicken tumor agent, or of the serums from chickens highly immune to the chicken tumors. AUTHORS' SUMMARY.

MEDULLO-EPITHELIOMAS OF THE BRAIN AND RETINA. T. B. DAVIE, J. Path. & Bact. **35**:359, 1932.

A medullo-epithelioma of the brain and two of the retina are described as examples of a subdivision of glioma and as examples of undifferentiated growth rather than of dedifferentiation.

THE BIOLOGY OF NEOPLASTIC CELLS. ALBERT FISCHER, Ann. d'anat. path. **8**:665, 1931.

This article by the leading continental student of tissue cultures is a condensed, scholarly résumé of the progress of oncology as a result of the study of tissues *in vitro*. His statements can be summarized as follows:

The classification of isolated cells in histologic sections is of no importance, because the topography of the cellular elements, not their form, is the essential in their identification. On the contrary, the culturing of tissue has taught the investigator to discriminate isolated cells according to their morphology. The method of tissue culture should not be regarded as a particular department, but merely as another method acquired by experimental medicine. Until recent days the study of cancer was in a state similar to that of the study of infectious diseases before the bacterial era. The technic of measuring the respiratory metabolism of neoplastic tissue and the culturing of tissues has enabled one to investigate the physiology of the cancerous cells.

The malignity of neoplastic tissue has its basis in a specific cancerous cell. One is not yet in a position to differentiate qualitatively between cancerous and normal cells. A method of culturing cells in conditions closely resembling those of the living organism has yielded precious data concerning the processes of regeneration and differentiation of normal cells.

The mechanism of illimited growth of neoplastic cells has become elucidated. The knowledge is based on measuring of the rapidity of growth and on the experiments performed by culturing together normal and neoplastic cells. The mutual influence between these two tissues could be observed with remarkable results.

It is of interest that colonies of cells the growth of which was very slow begin rapidly to proliferate as a result of insults caused to them by minute scratches (*petites blessures*).

Neoplastic cells possess a low resistance, and their life is short. There occurs a continuous destruction of neoplastic cells in tissue cultures.

In conclusion: the limitless proliferation of neoplastic cells in the organism is the physiologic result of the death of the malignant cells just as physiologic regeneration occurs as a result of damage to normal cells. B. M. FRIED.

CARCINOIDS OF THE SMALL INTESTINE. G. N. MARANGOS, Beitr. z. path. Anat. u. z. allg. Path. **86**:48, 1931.

In two of four cases of carcinoid of the intestine, there were metastases. All had a desmoplastic tendency, which contributed to the intestinal thickening and angulation. In all cases anaplasia was absent. Serial sections revealed the plexiform structure of carcinoids, and in all nodules above 2.5 mm. invasion of the walls of blood vessels with sheetlike spread beneath the endothelium was found. W. S. BOIKAN.

ENDEMIC HEMANGIOMATOSIS OF CHICKENS. J. SAL, Virchows Arch. f. path. Anat. **279**:62, 1930.

Many of the chickens of a chicken farm near Budapest suddenly became ill. Most of the fowls affected were from 6 months to 1 year old. The disease, which was fatal, was characterized by the development of soft, papillary, easily bleeding tumors at different parts of the skin. Necropsy revealed similar tumors in the liver, heart and lungs. Histologically, the tumor varied from cavernous hemangioma to hemangiosarcoma composed of cellular young tissue between the blood spaces. The sarcomatous tissue infiltrated and invaded the surrounding tissues. W. SAPHIR.

SYNOVIAL SARCOMA OF THE KNEE JOINT. P. PRYM, Virchows Arch. f. path. Anat. **279**:71, 1930.

Prym presents a detailed clinical and pathologic study of the case and reviews three others recorded in the literature. The synovial membrane was transformed into cellular tumor tissue with the morphology of spindle cell sarcoma. On the surface of the membrane were numerous papillary outgrowths covered by a single layer of high cylindric cells.

W. SAPHIR.

CLINICAL AND ROENTGENOLOGIC OBSERVATIONS OF THE JOACHIMSTHAL CANCER OF THE LUNG. A. BEUTEL and A. WOLDRICH, Ztschr. f. Krebsforsch. **34**:109, 1931.

In this report on the clinical and roentgen findings in the occupational pulmonary cancers of the Joachimsthal miners, there is included a series of roentgenograms of successive stages of the disease. Beutel and Woldrich conclude that there are two possibilities in the way of origin — either in a bronchial stem of the first order, with a form so flat as not to appear in the x-ray photograph, and with local consolidation representing a nonspecific pneumonia or spread of the cancer; or in a peripheral bronchial stem, with growth centrally and secondary involvement of the larger bronchi. They believe the latter to be the more probable mechanism.

H. E. EGGERS.

IS CHIMNEY-SWEEP'S CANCER REALLY EXTINCT? DUETSCHKE, Ztschr. f. Krebsforsch. **34**:159, 1931.

Although chimney-sweep's cancer is becoming so rare in Germany as to be virtually extinct, a recent case of this occupational cancer is reported.

H. E. EGGERS.

Medicolegal Pathology

INTERNAL CEREBRAL HEMORRHAGE DUE TO ACCIDENT. S. SHELDON, Brit. M. J. **1**:332, 1932.

A boy, aged 17, was knocked down by an automobile while he was crossing a road. He was picked up immediately and rushed to a nearby hospital while unconscious, where he died three hours later. There were abrasions on the backs of both hands and the fronts of the knees, a simple fracture of the middle third of the right tibia with much bruising, no scalp wounds or fracture of the skull, a little blood-stained fluid in the subdural space at the base of the brain, flattened convolutions, and an absence of injury or tearing of the outer surface of the brain. On sectioning the brain, a typical laceration with hemorrhage was found on the right side between the caudate nucleus and the optic thalamus, with free blood in both lateral ventricles. The ruptured vessels was on the right side. The remaining vessels were normal and free from atheroma.

WILLIAM FREEMAN.

SEVEN CASES OF GENERALIZED ARGYRIA. GERNEZ, HOUCKE and CUVELIER, Ann. de méd. lég. **4**:251, 1932.

A veritable epidemic of argyria was observed by the authors in patients suffering from pulmonary tuberculosis treated with collargol. The usual symptoms of nausea, vomiting, anorexia, abdominal pain and diarrhea accompanied the intoxication. These symptoms continued for several months after discontinuance of the injection of collargol. Silver was not found in the urine or in the blood, but it was present in the hair and in the nails of one patient. Chemical analysis of 10 cc. of bile did not reveal silver, but spectroscopic examination of this material

yielded positive results. The coloration developed after a latent period of about one year, during which time there were no other symptoms except digestive disturbances and progressive asthenia.

H. S. THATCHER.

PECULIARITIES OF MARKS OF CLOTHING ON LEAD BULLETS. H. PIÉDELIÈVRE, P. ÉTIENNE-MARTIN and G. PEIFFER, Ann. de méd. lég. **7**:477, 1932.

Bullets were placed on cloth held in front of a hard body and struck with a light blow from a hammer. Perfect imprints of the cloth were obtained, photographed and enlarged. These experiments were the controls. Bullets were then shot into a target of certain tissues in front of a block of paraffin. From these experiments the authors conclude that in principle a lead bullet takes the imprint of the first material which it traverses. It is able in certain cases to take the imprint of the second material, which is superimposed. The imprint of the first material happens to be modified also by the mixture with the others. Errors of identification are made, if one ignores the possibility of such a phenomenon.

H. S. THATCHER.

ANATOMIC INFERIORITY OF THE HUMAN ORGANS. W. A. NADESHDIN, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:426, 1932.

A study was made of the specific gravity of various organs with a benzene-chloroform mixture, in order to determine the differences between normal, pathologic and senile tissues. Acute poisonings, which selectively affect the blood vessels (cyanide, carbon monoxide, etc.), lower, for instance, the specific gravity of the aortic wall; sclerotic processes increase it. In poisonings, in general, the specific gravity of the parenchymatous organs usually appears lowered. The rigor mortis does not change the specific gravity of the muscle tissues. Since one finds in the kidneys 12 per cent blood, in the spleen 12.5 per cent and in the liver 29 per cent, these organs exhibit an increase in specific gravity in instances of death due to fatal hemorrhage. Tissues that have been preserved in a 10 per cent solution of formaldehyde do not materially differ from those just removed from the dead body.

E. L. MILOSLAVICH.

DETERMINATION OF BLOOD GROUPS IN CADAVERS. V. M. PALMIERI, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:446, 1932.

Group-specific properties of human blood do not disappear immediately after death, but persist for a certain period of time. The intensity of the cadaveric changes and the degree of temperature are important factors. The most satisfactory results are obtained up to the fourth day after death, provided the temperature at which the body is kept does not exceed 22 C. After the fifth day, the possibility of obtaining reliable results decreases gradually, especially if the temperature is high. In one instance, in which the body was kept for twenty days at a temperature of from 8 to 15 C., the blood group was satisfactorily determined. The average longest interval of time at higher degrees of temperature is, in general, not more than eight or nine days. Urinalyses for the group-specific properties constantly showed a negative result. In the pericardial fluid the agglutinins are detectable for a longer period of time, but they disappear faster than those in the serum. A few days after death, the red blood corpuscles lose their form and structure, and the receptors gradually vanish within from ten to fifteen days. The iso-agglutinins of the serum, however, persist at the same temperature for a longer time and are not demonstrable after from the fifteenth to the twentieth day. In old and disintegrated serum, new unspecific agglutinins, so-called panagglutinins, are formed, as the result of bacterial action, and may lead to false interpretations. Should the erythrocytes be nonusuable, an examination of the serum should be attempted, employing test erythrocytes A, B and O in lecithin suspensions.

E. L. MILOSLAVICH.

ACUTE POISONING WITH ZINC CHLORIDE. G. PFEIFFER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:1, 1932.

Up to the present, sixty-two instances are recorded in the literature, with a mortality of 60 per cent, death occurring on the day of poisoning in 40 per cent of the cases. The eschars exhibit a white-gray color, and the mucous membranes show a leather-like, shrunken appearance. The gross changes are somewhat similar to those observed in silver and mercury poisonings. The eschars may remain attached for a long period of time, and the sloughing process is not accompanied by a suppurative demarcation as in alkali poisonings. Later on, the local corrosive action of zinc chloride causes a very pronounced shrinkage of the affected structures, since this poison has the property of deeply and rapidly penetrating the tissues. An extensive shrinkage of the stomach often follows in nonfatal cases, and pyloric stenosis and anacidity are common complications. In contrast to other corrosive poisons, zinc chloride rarely gives rise to perforation of the stomach. If the poison was ingested, signs of corrosion in the mouth, pharynx and esophagus are frequently absent. The longer the victim survives, the more marked are the inflammatory changes in the kidneys. The clinical picture does not contain any symptoms characteristic of zinc chloride poisoning. Violent vomiting and hypersecretion are caused by severe acute gastritis.

E. L. MILOSLAVICH.

CHANGES IN THE PAPILLARY MUSCLES OF THE HEART IN ILLUMINATING GAS POISONING. W. RADTKE, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:26, 1932.

In poisonings by illuminating gas, characteristic changes are found in the papillary muscles of the left ventricle of the heart, consisting of irregularly distributed areas of hemorrhages, inflammatory reactions and necrosis. These lesions are chiefly met with in the apical portion of the muscles, but may also involve their basal segment. The papillary muscles of the tricuspid are not affected. These findings are observed in cases of a protracted course of carbon monoxide poisoning, being most pronounced if death followed twenty-four hours, or longer, after the exposure. From a medicolegal point of view, these changes in the papillary muscles are of great practical significance, since in a case of death from an obscure cause their detection at autopsy will direct attention to carbon monoxide exposure, as illustrated by two very interesting observations.

E. L. MILOSLAVICH.

TEARING OF THE INTIMA OF THE COMMON CAROTID CAUSED BY STAB WOUND OF THE NECK. J. FAZEKAS, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:54, 1932.

At autopsy in the case of a 52-year-old man who committed suicide, three stab wounds of the neck were found. The instrument used was a blunt pocket knife. The left common carotid showed, 4 cm. below its bifurcation, a transverse tear in its intimal surface, 6 mm. in size, while the artery otherwise appeared not perforated. The instrument had caught in the corner of the carotid bifurcation and had distended the vessel upward and backward, causing the intima to tear transversely below the actual point of acting force. A transverse intimal tear, as in death by hanging, is the result of a force that elongates or longitudinally distends the blood vessel, while compression alone causes axial or longitudinal laceration of the intima.

E. L. MILOSLAVICH.

SIGNIFICANCE OF FOREIGN MATERIAL IN THE INTESTINES OF THE NEW-BORN INFANT IN PROVING INFANTICIDE. K. BEOETHY, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:58, 1932.

If a dead body is submerged, water or other fluid mediums may arrive in the stomach, but will not pass the pyloric barrier, except in instances of abnormally

high pressure. Presence of water or other fluid with foreign material suspended in it, below the pyloric ring, is a positive indication that the person was submerged while still alive. Experiments performed on twelve dead bodies of newborn infants proved this important fact. E. L. MILOSLAVICH.

SWALLOWING OF FOREIGN BODIES BY IMPRISONED CRIMINALS. R. GOEDEL, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:63, 1932.

Nineteen cases are described and psychologically analyzed, disclosing persons of hysterical and psychopathic character, only one fourth of them expressing suicidal intent. In 50 per cent of the cases, repeated ingestion of foreign bodies was observed. Evasion of disciplinary punishment or dodging of assigned prison work was the common driving motive. E. L. MILOSLAVICH.

ATTEMPTED SUBSTITUTION OF ANOTHER PERSON IN PATERNITY BLOOD TEST. A. LAUER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:79, 1932.

The father of the child tried to deceive the expert by sending to the laboratory in his stead a friend for the blood testing ordered by the court. Since in the laboratory every person to be examined is photographed for the purpose of record, a deception was readily prevented. It is suggested that, as a routine, fingerprints also be taken of all persons subjected to this examination of the blood in order to eliminate any possible error or imposition. E. L. MILOSLAVICH.

DISSIMULATION OF A SEVERE GUNSHOT WOUND OF THE HEAD. W. LESCHMAN, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:82, 1932.

With suicidal intent, an innkeeper shot himself in the right temporal region, at first with no ill effects. He kept the incident secret and continued his regular work for two days and then called a doctor because of grip, coughing and headache. The doctor incidentally discovered the wound, which was concealed under a small piece of adhesive tape. On account of increasing intracranial pressure, trephining was done on the third day, and crushed brain tissue and blood clots exuded. Stereoscopic pictures disclosed the bullet on the opposite side within the skull. Recovery followed. E. L. MILOSLAVICH.

SEXUAL PERVERSIONS LEADING TO FATAL ACCIDENTS. F. SCHWARZ, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:85, 1932.

Accidental death may unexpectedly occur by interference of unforeseen or unintentional incidents during acts committed because of a perverted sexual instinct. Often the findings at the scene of the accident are baffling and may then be easily misinterpreted and a murder assumed. Certain cases of death by hanging are not suicides but are accidental deaths, as the victim tried, by the act of hanging, to stimulate and increase his sexual orgasm. A young man while sitting in a bathtub at night was looking at some obscene pictures and got hold of a defective electric lamp placed on a chair nearby. Electrocution caused death. The lamp was found submerged in the bathtub, and the man's lungs showed some aspiration of water. A second case involved a young person with transvestitistic perversion, who was found dead in his bedroom dressed only with ladies' stockings and a garter supporter showing dried sperm spots. Various articles of women's underwear were neatly stored in his dresser. Death occurred from carbon monoxide poisoning due to an open jet of a gas stove, the flame of which had been put out by the stormy wind blowing through an adjoining chimney flue.

E. L. MILOSLAVICH.

Society Transactions

BUFFALO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Nov. 4, 1932

KORNEL TERPLAN, *President, in the Chair*

STUDIES OF PLASMA PROTEINS. J. LOESCH.

The relationship between changes in the plasma proteins and damage to the kidneys produced in dogs in two different ways was studied. Ischemia of the kidneys produced by clamping the renal pedicle was followed by a rise in the plasma fibrinogen. This was noted when both kidneys were treated in a normal animal or when one kidney was manipulated six months after a unilateral nephrectomy. This effect was not obtained during the terminal condition, when a marked retention of nitrogenous products had taken place.

I believe that the increase in fibrinogen was due to stimulation of the liver, and that the decrease in the terminal condition was a result of impaired function of the liver brought about by the retained waste material.

If the renal pedicle was not manipulated, animals from which as much as three quarters had been removed showed no change in plasma fibrinogen after the immediate effects of operation had passed. The only change noted in this group of dogs was an increase in the plasma albumin, which was not great in any instance, but was regularly observed when diets high in protein were fed. As this increase paralleled slight variation in the cells it seemed probable that it was caused by decreased hydration of the blood.

RECURRING JAUNDICE WITH REPORT OF BIOPSY. S. SANES.

Several days following a gastro-intestinal upset consisting of nausea and emesis, abdominal cramps and diarrhea, deep jaundice developed rather acutely in a white woman, aged 38. Six months previously, the patient had received an intravenous injection of arsphenamine (0.2 Gm.) at three weekly intervals; no untoward symptoms were experienced. Physical examination revealed, in addition to jaundice, only a palpable liver. No evidences of syphilis were demonstrated. The temperature ranged from 99 to 99.5 F. Laboratory studies made at various times during the patient's illness yielded information as follows: icteric index, from 100 to 75; van den Bergh test, immediate reaction positive, from 62 to 6 units; bromsulphalein test, 100 per cent retention after thirty minutes; urobilin in urine, from 2 plus to 0; Wassermann reaction, negative; duodenal drainage, bile-positive; leukocyte count, not significant; culture, no pathogenic bacteria. In the fifth week of her illness, the patient was seized with a severe pain in the upper part of the abdomen accompanied by emesis. Laparotomy disclosed the liver and spleen distinctly enlarged, the gallbladder apparently normal, the bile ducts not dilated, and an absence of stones. A small piece of liver was excised. The jaundice gradually decreased postoperatively until, four months after onset, icterus could not be detected in the skin or in the sclerae. It reappeared on two later occasions for several days in relation to gastric distress. Six months after the initial complaints, the patient was symptomatically well and showed no jaundice in skin or sclerae; the liver was not palpable; the bromsulphalein test showed no retention of dye after thirty minutes; the van den Bergh test showed 1.5 units.

The excised piece of liver measured 1 by 0.8 by 0.3 cm. Microscopic examination revealed in a small area a fairly well preserved architecture. In the remaining portion of the specimen normal structure was absent; the lobules appeared collapsed. The histologic picture showed different stages of regressive change, restricted almost solely to the hepatic parenchyma. In the still preserved lobules, the cells demonstrated varying degrees of degeneration, as evidenced by swelling, poor staining properties, coarse granules, vacuoles and indistinct cell outlines. Nuclei in degenerating cells showed different phases of karyolysis. In certain cells, nuclei were large and extremely dark. Cells with many nuclei were also observed. In some lobules, the cells in the central zone were necrotic, often

containing yellowish-green pigment. The Kupffer cells were somewhat swollen. Scattered cellular débris and nuclear particles were present. The portobiliary spaces showed an apparent increase of small bile ducts and capillaries, with infiltration by leukocytes, occasional plasma and eosinophil cells, and large oval cells possessing pale, spindle-shaped nuclei. Collapsed lobules were irregular in shape and size. Hepatic columns could not be followed distinctly. Sinusoids were dilated and filled with blood. Scattered in the remaining reticulum were many leukocytes, eosinophils and oval cells with dark round and kidney-shaped nuclei. No mitoses and no definite proliferation of connective tissue could be made out. The large bile ducts contained no exudate or desquamated epithelium. There was no inflammatory reaction in their walls. No bile thrombi were noted.

The histologic changes were explained on the basis of a toxic dystrophy of the liver of a mild but slowly progressive and intermittent character. Comparisons were made with the findings observed in so-called catarrhal jaundice (Eppinger, Bauer, Klemperer) and in subacute toxic atrophy. In view of the lack of demonstrable evidence of syphilis, the recent nature of the hepatic changes and the length of time following administration of the drug, it was doubted whether arsphenamine alone could be the principal causative factor.

SUPRARENAL HEMORRHAGE IN ADULTS. RAYMOND S. ROSEDALE.

Suprarenal hemorrhages in adults are fairly well recognized (Seligman, Kraus, Goldzieher, Dietrich and Siegmund). The unilateral type of hemorrhage occurs less frequently than the bilateral, with a clinical picture not dissimilar. The massive unilateral hemorrhage as a primary cause of death is comparatively rare. In such cases, death probably results from extensive hemorrhagic infiltration of the perirenal and retroperitoneal tissues, and not from suprarenal insufficiency, because even in the involved gland there is often found fairly well preserved parenchyma. Death must then be interpreted on the basis of a shocklike result, such as occurs in any extensive retroperitoneal hemorrhage.

CASE 1.—A white man, aged 36, a chauffeur, while loading and transporting 2 tons of coal in a wheelbarrow, suddenly experienced sharp pain in the right costovertebral angle, causing him to rest. This discomfort persisted and was followed six hours later by epigastric pain and vomiting. When he was admitted to the Buffalo City Hospital, the upper part of the abdomen was tender and rigid. The leukocyte count was 19,000, 79 per cent being polymorphonuclears. The temperature was 100 F. The blood pressure slowly fell. Because of the progressive shock with severe abdominal pain and vomiting, acute hemorrhagic pancreatitis was suspected, and a laparotomy was performed. Death occurred seventy-six hours after the onset of pain.

At autopsy, the right suprarenal gland was found involved by an extensive hemorrhage. This had destroyed nearly the entire cortex, leaving only thin remnants, and had infiltrated the retroperitoneal tissues downward as far as the pelvic brim, over the pancreas and to the left as far as the hilus of the spleen. There was a soft apparently recent thrombus in the right suprarenal vein.

The histologic picture showed only the changes reactive to severe hemorrhage, such as infiltration by leukocytes. There was necrosis of some of the cortical cells, but, on the whole, cortical and medullary parenchyma was well preserved. Stain for bacteria proved negative.

There were no signs of a primary inflammation in the suprarenal gland itself, nor any thrombophlebitis or thrombosis in the smaller veins of the medulla. It is felt that the recent thrombosis found in the right suprarenal vein was secondary to the extensive hemorrhage.

The usual causes of suprarenal hemorrhages as mentioned in the literature are lacking in this case. The exact cause is not clear. Kraus and others described a mechanical factor involving traction on the hilus of the suprarenal gland due to prolonged contraction of the musculature of the suprarenal vein. They stated their belief that this may cause a rupture of the suprarenal capillaries with acute extensive hemorrhage, as in apoplexy. Because of the definite history of unusual exertion in a person unaccustomed to hard labor, the question arises whether or not the mechanism described by Kraus might have been an important factor in this case.

CASE 2.—In a white man, aged 24, bilateral suprarenal hemorrhage was found. It was not extensive, and there was no destruction or infiltration of the tissues about the gland. The hemorrhage in this case was explained rather on an infectious basis, as chronic gonorrheal urethritis, prostatitis and dermatitis were present. Here the hemorrhage occurred six hours after the passage of a catheter through a urethral stricture.

Many believe that marked suprarenal hemorrhage may occur in a condition of general infection, in which the capillaries of the suprarenal medulla are subjected to extensive diapedesis of erythrocytes. Although a purulent inflammation of the bladder, prostate and skin was present in the second case, I feel that the so-called infectious theory is not sufficient in order to understand the sudden extensive hemorrhage, as there still must be explained why the bilateral hemorrhage followed rather acutely the forceful and very painful passage of a urethral catheter.

MARKED ENLARGEMENT OF THE HEART IN INFANCY DUE TO PARENCHYMATOUS MYOCARDITIS. F. E. KENNY.

Two cases of marked dilatation and hypertrophy of the heart in infancy have been studied. Other instances of such cardiac enlargement have been reported, which were termed idiopathic enlargement. Stoloff, in 1927, completely reviewed this subject. These other cases were so called, because of the obscurity of the etiology and the lack of microscopic changes in the myocardium. A careful study of such published reports has revealed, however, in a few instances, degenerative changes and increased connective tissue in the myocardium. Other cases have been reported which occurred in infants and in which true myocarditis was present. In both cases presented here, I wish to stress the history of previous infection and the presence of parenchymatous degeneration of the myocardium.

CASE 1.—A white girl, aged 12 months, had a history of pneumonia six weeks previous to hospitalization. Fatal illness was ushered in by dyspnea, cough and loss of appetite. Autopsy showed the heart to be markedly dilated and slightly hypertrophied, weighing 85 Gm. No congenital abnormalities were found.

Histologic examination revealed a diffuse parenchymatous degeneration throughout the cardiac muscle. The muscle fibers were swollen; cross and longitudinal striations were absent. The cytoplasm was not well stained and showed in some places granular degeneration. Here and there only the sarcolemma remained, enclosing cellular débris, while in other places, no remnants of the muscle fibers could be found. The nuclei were chiefly eccentric in position, with many variations in size and staining qualities, and with chromatin material scattered throughout the nuclear substance. In the outer layers of the myocardium, beneath the epicardium, were many round cell infiltrates, most of the degenerative process being in the inner layers. Fibrous tissue did not seem to be increased in amount.

CASE 2.—A white boy, aged 6 months, had been perfectly well until 3 months of age, and then had suffered from stomatitis and attacks of dyspnea and cyanosis. Three months after the first illness, his condition became more serious; he refused feeding, and became dyspneic and cyanotic. Pericarditis with effusion was diagnosed, and the pericardium was tapped, a slight amount of bloody fluid being withdrawn. Death followed shortly after the paracentesis. Autopsy revealed compression atelectasis of the lungs and marked dilatation and moderate hypertrophy of the heart, which weighed 65 Gm. No congenital abnormalities or vascular anomalies were present.

Microscopically, the endocardium was distinctly thickened. The inner zone of the cardiac muscle showed a patchy degeneration of the myocardium, characterized by pale-staining cytoplasm, and in some places, only the sarcolemma remained. The outer zone showed a marked increase in interstitial fibrous tissue. No cellular infiltration was present.

These two cases of apparently toxic myocardial degeneration seem to be directly traceable to previous infection. In the first case, there was a fairly recent inflammatory condition (pneumonia) with the resulting active process in the cardiac muscle; in the second instance, the infection was more remote, the degenerated areas having been partially replaced by fibrous tissue.

Book Reviews

The Intervertebral Discs: Observations on Their Normal and Morbid Anatomy in Relation to Certain Spinal Deformities. By Ormond A. Beadle. Medical Research Council, Special Report Series, No. 161. Price, 2 shillings, net. Pp. 179. London: His Majesty's Stationery Office, 1931.

The author presents a summary of the work by Schmorl and his students on about seven thousand spines, and his own observations after examining the same material. His own ideas are, however, in harmony with Schmorl's interpretations. The many illustrations have been supplied by Professor Schmorl.

The section on anatomy discusses the nature of the end-surfaces of the adult vertebral bodies and the construction of the intervertebral disks. The part played by the periphery of the annulus in conjunction with the epiphyseal ring is pointed out.

The section on the adolescent spine gives an account of the normal development, and points out how the different appearance of the growing spine may be explained in relation to the adult structures. Close reading will help to clear up the debated subject of vertebral epiphyses in man.

The discussion on malformations of the intervertebral disks discloses the not infrequent, but little known, developmental defects: persistence of chorda tissue, nuclear expansions of the disks and breaks in the cartilage plates.

Next is a review of the degenerative changes of the fibrous structure of the disks. Changes which in other organs would be interpreted as advanced degenerations occur in the intervertebral disks with surprising frequency, and seem to set in comparatively early. Examination of a large series of spines leaves the impression that in the middle decades of life, as well as later, well preserved disks are the exception rather than the rule. It is pointed out that the changes which may lead to complete loss of function are to be regarded as the results of continued excessive functional strain on tissues which, in the course of increasing age, have become lifeless and desiccated and are no longer able to withstand the burden of activity or to react to adaptation and repair.

It is pointed out that the cartilage plates are subject to a series of changes which are partly further developments of the processes in the fibrous portions of the disks, and partly primary. In general, the cartilage plates are the most resistant parts of the disks, and their important function is to protect the spongiosa, which is provided with no end-plate of compact bone, like the long bones, against the pressure of the nucleus and the tension of the fibers of the annulus lamellosus. The cartilage serves to confine the tissue of the disks to its proper limits and to maintain its normal form and turgor. The plates may be injured by direct trauma and by disease causing advancing destruction of the vertebral body, but under such circumstances the plates show evidence of resistance to destruction. The most common change in the cartilaginous plate is the development of lack of resistive power. As long as the plate is intact, the disk may still perform its work with fair efficiency, even though severely injured in its substance.

The next section discusses prolapse of disk tissue into the spongiosa, and points out that as soon as the cartilage plate gives way, a series of most remarkable changes takes place with a great degree of deformity of the disks. When a break in the continuity of the plate occurs, the turgid nuclear substance passes out into the spongiosa. Such a prolapse causes the disk to lose substance and upsets the stress and strain relations within it. The process slowly limits itself by protective reactions, in young persons mostly through the proliferation of cartilage and bone. In adults, the damage is usually more severe, and granulation tissue invades the disks and they may ossify, and the disks are practically destroyed. Thus the mechanical shocks transmitted during hard work from part to part of the spine are no longer absorbed by the elastic cushions of the disks and strike now

against almost bare bony surfaces. In this way great injuries to various parts of the spine are caused and serious deformities arise.

The eighth section deals with lesions of the disks of external origin, particularly from disease or injury of the vertebral bodies. The effects of trauma, slight shocks of normal life, fractures of vertebral bodies and lesions due to disease are discussed.

The ninth section concerns spinal deformity. The various degenerations and injuries to the disks are nearly always found associated with degrees of spinal curvature, but the large and important group of scoliosis must be excluded here. No definite relation between scoliosis and the changes in the disks has been established. On the other hand, the changes are found to be typical and constant phenomena in various other simpler deformities, notably the kyphoses of youth and age and the growth of senile degenerative disabilities known under the term of spondylosis deformans. According to the author, the clearest division that has yet been made of the kyphoses is a group developing in the young, before the close of growth, and a group occurring in middle and later life.

The kyphoses of adolescence form a fairly well defined group, and appear from the twelfth year onward. These kyphoses are distinguished by characteristic prolapses of the disk in the nucleus region in the lower dorsal spine, a lower dorsal kyphosis and a correspondingly highly developed lumbar lordosis. The curvature is due to the vertebral bodies being wedge-shaped—definitely narrower in front than behind. Senile kyphosis is characterized by a curvature, and in the pure cases the intervertebral disks in the greater part of their extent are well preserved, the various forms of senile degeneration are absent, and the cartilage plates are uninjured except at the anterior ends in the kyphotic segment. The kyphosis is different from that of adolescence in that it exists preeminently in the upper or middle dorsal region.

Spondylitis deformans is then discussed. The kyphosis, although almost always present, is not looked on as an integral part of the disease, but rather as an admixture of a coexistent senile kyphosis. Extensive degenerative changes in the intervertebral disks may be considered as the fundamental lesion of spondylitis deformans. It is the typical senile disease of the spine. The sequel, so far as the spine is concerned, is first an increased movability of the vertebrae on one another, owing to the dissolution of the normal disk fibers. Then, when the disks are fibrosed, there sets in a generalized stiffening of the spine which may proceed to a bony ankylosis. It is conceived that during this earlier stage of greater movability, the osteophytes are formed. These osteophytes are present in practically all cases of spondylosis in greater or lesser degree and give the spine a characteristic appearance. They may grow to an enormous size, and contiguous projections may fuse. They do not occur on the posterior surface of the spine, so that narrowing of the spinal canal and consequent nerve changes do not occur.

It is pointed out that when the aging person escapes senile kyphosis and spondylitis deformans he is liable to develop senile osteoporosis of the spine. The site of the lesion is in the spongiosa, and the disks may be well preserved in spite of great age. The intervertebral disks bulge into the atrophic spongiosa above and below.

Mention is made of Bechterew's disease of the spine. It is supposed to be an ostearthritis of the small intervertebral joints which results in a complete but smooth ossification of the anterior longitudinal ligament without osteophytes or bony protuberances of any kind. The whole spine is converted into a hollow tube with a structure resembling that of the ordinary long bones, with, however, only a thin layer of compact bone in front. A varying degree of kyphosis is also present.

It would be difficult to express the debt which the medical profession owes to Dr. Beadle for summarizing so lucidly and so completely the extensive work of Schmorl and his co-workers. At a time when anatomy is considered dead and when pathologic anatomy is said to have exhausted itself, Schmorl turns his attention to a subject of greatest clinical importance and clearly points a way to a

Book Reviews

The Intervertebral Discs: Observations on Their Normal and Morbid Anatomy in Relation to Certain Spinal Deformities. By Ormond A. Beadle. Medical Research Council, Special Report Series, No. 161. Price, 2 shillings, net. Pp. 179. London: His Majesty's Stationery Office, 1931.

The author presents a summary of the work by Schmorl and his students on about seven thousand spines, and his own observations after examining the same material. His own ideas are, however, in harmony with Schmorl's interpretations. The many illustrations have been supplied by Professor Schmorl.

The section on anatomy discusses the nature of the end-surfaces of the adult vertebral bodies and the construction of the intervertebral disks. The part played by the periphery of the annulus in conjunction with the epiphyseal ring is pointed out.

The section on the adolescent spine gives an account of the normal development, and points out how the different appearance of the growing spine may be explained in relation to the adult structures. Close reading will help to clear up the debated subject of vertebral epiphyses in man.

The discussion on malformations of the intervertebral disks discloses the not infrequent, but little known, developmental defects: persistence of chorda tissue, nuclear expansions of the disks and breaks in the cartilage plates.

Next is a review of the degenerative changes of the fibrous structure of the disks. Changes which in other organs would be interpreted as advanced degenerations occur in the intervertebral disks with surprising frequency, and seem to set in comparatively early. Examination of a large series of spines leaves the impression that in the middle decades of life, as well as later, well preserved disks are the exception rather than the rule. It is pointed out that the changes which may lead to complete loss of function are to be regarded as the results of continued excessive functional strain on tissues which, in the course of increasing age, have become lifeless and desiccated and are no longer able to withstand the burden of activity or to react to adaptation and repair.

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better understanding of spinal structural changes. The monograph is beautifully illustrated and should be in the hands of anatomists, who could profitably introduce some of these problems to the medical student in the osteology courses. Orthopedists as well as surgeons and physicians will be interested in the new knowledge about the intervertebral disks.

Physiology of Bacteria. By Otto Rahn, Professor of Bacteriology, Cornell University, Ithaca, N. Y. Cloth. Price, $6. Pp. 438, with 42 illustrations. Philadelphia: P. Blakiston's Son & Co., 1932.

Professor Rahn's intention in writing this book was to coordinate the physical and chemical knowledge of the necessary functions of life. Among the numerous processes of living organisms he has singled out four functions as essential to life. These are endogenous catabolism, energy formation, growth and death. The book is limited to a discussion of these, omitting considerations of motility, phosphorescence, tropisms, morphology, reproductive processes and similar functions.

The plan of the book is original and unique. It is not a review of the literature, although its text and twenty pages of bibliography make it useful as a reference book. It contains a careful analysis and mathematical treatment of the published quantitative results of the experiments of many investigators, together with numerous hitherto unpublished experiments of the author. It is highly critical in the analysis of data and theories, but "in order to counterbalance any personal view-point, each chapter and subchapter contains a summary usually separated according to facts and theories."

As the title indicates, most of the material has been drawn from studies of bacteria. Pertinent material from studies of other lower fungi has been used also, particularly the results of many important investigations of the physiology of yeast. The title by no means indicates the limitations of the scope of the book. The author clearly shows how wide are the ranges of bacteriologic processes and how advantageous these organisms are for investigations in cellular physiology. There is increasing agreement with the opinion of the author that general physiology has much to learn from the physiology of the bacteria, and that the principles set forth in this book reach beyond the domain of bacteriology and apply to biology generally.

The first section of eleven pages is a discussion of endogenous catabolism, the deterioration of cell compounds within the cell. A distinction is made between the autolytic digestion of dead cells and the products arising from the constant deterioration of protoplasmic parts of the cells due to the instability of enzymes and other compounds.

The second section gives an account of the sources of energy for the cell and deals chiefly with fermentation. Fermentation is broadly defined as "the chemical decomposition of compounds within the cell for the purpose of liberating energy." This includes all the intracellular decomposition processes, organic and inorganic, aerobic and anaerobic, with and without gas, of fats, carbohydrates, proteins and other compounds which yield energy. Quantitative data on energy exchange and equations for many types of fermentation are set forth in appropriate groups. The measurements of energy exchanges show that a considerable amount of energy is required to produce the cells of yeast and bacteria from foodstuffs and for the maintenance of energy potentials in the living cell to prevent detrimental reactions. The author adopts the opinion that most of the reactions of fermentation can be explained best by the assumption that the enzymes of the cell activate certain hydrogen atoms in the substrate. These then combine with a hydrogen acceptor, which may combine with another part of the same molecule, with another organic or inorganic molecule or with activated oxygen. The chapters following this section present a critical analysis of the rôle of oxygen in all fermentations.

The third section, on "Growth," discusses chiefly the function of the construction of complex molecules from less complex and the resultant total increase of the living substance of the cell. Processes of growth are separated from fermentation as sharply as possible in the study of a function which is ultimately dependent

on fermentative energy exchange. The author finds that fermentation and respiration are brought about by catalysts of one kind (enzymes), and that multiplication is under the control of catalysts of another kind (genes). Visible morphologic formations are not discussed in this section, but the author has much of interest to say about the probable molecular configurations and arrangements in the living cellular substance.

Data on the death rates of bacteria under a variety of conditions are assembled and analyzed in the fourth section of the book. This contains much valuable information about the action of disinfectants. Through his analysis of the logarithmic order of death of bacteria, the author recapitulates and develops his ideas of the mechanism of death as a continuous chemical process which becomes irreversible when one essential molecule becomes decomposed. "If the order of death is computed under the assumption that the destruction of one certain molecule in the cell is sufficient to prevent growth, the resulting order of death corresponds to that observed with bacteria of uniform age."

Although the book is intentionally restricted to the consideration of the four functions selected by the author as fundamental in the physiology of bacteria, the ramifications of the discussions lead to the examination of many other partial functions. It is not an exposition of the whole of bacterial physiology, but does cover a large part of the field. It is evident that information obtainable by experiment is needed on many subjects included in the sphere of this book. The book seems certain to influence future researches, both through its indication of problems requiring investigation and through investigations it will provoke to test theories and conclusions supported by the author but not accepted by others.

The thoughtful and broad point of view of the author and his mastery of the material give the book an original and individual quality. The reviewer was deeply interested and stimulated by reading it. The publisher is to be thanked for his part in making the book available.

Handbuch der Blutgruppenkunde. Bearbeitet von Dr. H. Bürkle-de la Camp, Privatdozent, Oberarzt der chirurgischen Universitätsklinik, Munich; Dr. M. Hesch, Assistent am anthropologisch-ethnologischen Forschungsinstitut der Universität Leipzig; Dr. G. Raestrup, o. Professor, Direktor des Institutes für gerichtliche Medizin der Universität, Frankfurt a.M.; Dr. E. D. Schött, Facharzt für Haut- und Geschlechtskrankheiten; Dr. P. Steffan, Marinegeneraloberarzt, Chefarzt des Marine-Lazaretts, Wilhelmshaven; Dr. O. Thomsen, o. Professor, Direktor des Instituts für allgemeine Pathologie, Kopenhagen; I. S. Wellisch, Senatsrat, Wien. Herausgegeben von Dr. Paul Steffan Marinegeneraloberarzt und Chefarzt des Marinelazaretts Wilhelmshaven. Price, 48 marks. Pp. 669, with 125 illustrations and 3 charts. Munich: J. F. Lehmann, 1932.

This handbook on blood grouping consists of 9 parts and 2 appendixes. In the first part Michael Hesch of the anthropologic-ethnologic research institute of the University of Leipzig traces the unbroken course of progress in blood grouping from 1901, when Landsteiner described the existence of human blood groups. The second part, which deals with the serology of blood grouping in man and animals, is written by Oluf Thomsen, professor of general pathology in the University of Copenhagen, who also wrote part 4, on the relations between the blood groups and other hereditary characters, but particularly morbid conditions of various kinds. The inheritance of the factors of blood grouping is discussed in part 3 by Siegmund Wellisch, engineer and Senatsrat in Vienna, who is an active investigator in this field. The practical use of blood grouping in transfusion and transplantation is presented in detail, clinical and operative, by Bürkle-de la Camp of the surgical clinic of the University of Munich. Perhaps more attention should have been given in this section to the actual, practical problems of selecting and controlling donors under various conditions. Part 6, by G. Raestrup, director of the medicolegal institute of the University of Frankfurt a.M., is devoted to blood grouping in legal medicine. Paul Steffan, the editor, Marinegeneraloberarzt in Wilhelmshaven, wrote part 7, on the distribution of the blood

groups in the various human races with reference to its bearing on racial origins. Part 8, the technic of blood grouping, is by Dr. E. D. Schött of Stockholm. These parts or sections constitute separate comprehensive monographs by authoritative writers on the main fields of blood grouping. Part 9, by Michael Hesch, contains the bibliography of blood grouping to 1931; 2,979 titles are given, arranged alphabetically by authors' names and covering 98 pages. The appendixes by S. Wellisch contain tables of squares and square roots, in order to facilitate the calculations of indexes. There is a complete subject index at the end.

The book summarizes conveniently and thoroughly what is known about blood grouping and its application for practical and scientific purposes. The component parts are well balanced and coordinated. It is a great central storehouse of information. This handbook and Lattes' "Individuality of the Blood," recently translated into English by L. W. Howard Bertie (Oxford University Press), fully meet the present need of investigation and practical work for comprehensive presentations of blood grouping.

Primary Carcinoma of the Lung: Bronchiogenic Cancer. A Clinical and Pathological Study. In Two Parts. By B. M. Fried, M.D., Peter Bent Brigham Hospital, Boston. Price, $5. Pp. 247, with 95 illustrations. Baltimore: Williams & Wilkins Company, 1932.

This addition to "Medicine Monographs," presented as a clinicopathologic review, serves once more to bring into prominence the increasing importance of cancer of the bronchi as a disease entity. The author considers the various histogenetic theories in detail, and presents convincing arguments in favor of the view that all pulmonary carcinomas probably arise from the basal cells of the bronchial mucosa, and that the advanced differentiation of some tumors is the result of a form of metaplasia of these cells.

Besides the article as it originally appeared in "Medicine," the book contains the details of all the case studies on which the report is based. This additional material comprises 102 of the 234 pages of reading matter, and is divided into two groups, the one of "typical" instances, in which the correct diagnosis might possibly have been suggested by the bronchopulmonary symptoms, and the other of an "atypical" group, in which the disease was characterized by symptoms other than those calling attention to the lungs. In the latter group, the records of tumors the first symptoms of which were due to cerebral metastases are particularly illuminating. Many such patients had undergone operations for removal of the tumor in the brain. The subsequent history of these patients seems to indicate that such a procedure is often valuable as a palliative measure, and that the knowledge that an intracranial growth is secondary to a bronchial carcinoma should not, in itself, contraindicate an attempt to remove the metastasis.

The value of the work is greatly enhanced by an abundance of excellently reproduced illustrations of gross and microscopic lesions and roentgenograms. The format is attractive, although typographic errors appear with the usual frequence in the volumes of this series. Appended are a list of references and an index.

The book should be especially helpful to physicians, who will find in the descriptions of some of the more bizarre manifestations of the disease many suggestions of aid in diagnosis.

Fungous Diseases: A Clinico-Mycological Text. By Harry P. Jacobson, M.D., Attending Dermatologist and Member of the Malignancy Board, Los Angeles County General Hospital. With an Introduction by J. Frank Schamberg, M.D., Professor of Dermatology and Syphilology, Graduate School of Medicine, University of Pennsylvania, and Howard Morrow, M.D., Clinical Professor of Dermatology, University of California Medical School. Price, $5.50. Pp. 290, with 153 illustrations. Springfield, Ill.: Charles C. Thomas, 1932.

This treatise brings up to date a summary in textbook form of the clinical and scientific aspects of the important mycotic diseases affecting the human species.

It is a practical reference book, and a timely one, on classification, diagnosis, prognosis, technic and therapy, and is arranged for easy reference. The book offers to the practitioner and the medical student a comprehensive discussion of this subject, a feature which alone should make it welcome. The book is practically complete in the light of present knowledge, and is well written. All pertinent literature is included in the bibliography of each subject, and credit is given where it is due. The author has borrowed freely of photographs, and, for the most part, the illustrations are good. It is noticeable that the recent findings of mycotic nature in perlèche of the types seen both in children and in adults are not included in this book.

The contents are divided into ten chapters, but into three major divisions, a logical grouping. These divisions are: (*A*) primary cutaneous mycoses with (usually) no definite systemic involvement (this includes the dermatomycoses, comprising all forms of ringworm and favus); (*B*) primary cutaneous and mucous membrane infections with frequent systemic involvement (moniliasis, mycetoma, sporotrichosis, blastomycosis, actinomycosis and coccidioides), and (*C*) primary systemic infections with occasional instances of cutaneous or mucous membrane involvement, including torulosis and aspergillosis.

Clinical Endocrinology of the Female. By Charles Mazer, M.D., Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania; Gynecologist to Mount Sinai and Northern Liberties Hospitals, Philadelphia, and Leopold Goldstein, M.D., Demonstrator of Obstetrics, Jefferson Medical College; Assistant Gynecologist to Mount Sinai Hospital. Price, $6, net. Pp. 518, with 117 illustrations. Philadelphia: W. B. Saunders Company, 1932.

The purpose of this book is to review the knowledge of the relations between the female generative functions and the endocrine secretions, with particular reference to the application of that knowledge in clinical diagnosis and treatment. The book opens with an introductory section followed by two comparatively long chapters on the ovary and its hormones and on the pituitary gland and its hormones. Then come briefer considerations of the thyroid and other endocrine glands and of endocrine relationships. The clinical value of the tests for ovarian and pituitary sex hormones in the blood is reviewed, with descriptions of the technical details. Chapters 8 to 11 deal with menstruation, its disorders and their treatment with glandular products in particular. There are chapters on functional sterility, endocrine regulation of pregnancy and labor, the hormone tests for pregnancy, lactation, the rôle of the hormones in the menopause, ovarian transplantation as a therapeutic measure and endocrine obesity. The book closes with a list of 649 references, an author index and a subject index. The chapter on the hormone tests for pregnancy will be of value to those who make such tests. The influence of the luteal hormone on the endometrium will interest the pathologist who studies uterine scrapings microscopically. The developments in the endocrinology of the female sex invest the pathologic anatomy and histology of the female reproductive organs with a new interest. The treatment of the various topics is sensible and conservative. There is no tendency to exaggeration or mysticism. The style is clear; the illustrations are commendable. In all writings on clinical endocrinology special care should be given to the choice of names to designate various endocrine products, in order to avoid confusion.

Books Received

A HANDBOOK OF EXPERIMENTAL PATHOLOGY. By George Wagoner, M.D., Associate in Pathology, and R. Philip Custer, M.D., Associate in Research Pathology, University of Pennsylvania. Price, $4. Pp. 160. Springfield, Ill.: Charles C. Thomas, 1932.

POLIOMYELITIS: A SURVEY MADE POSSIBLE BY A GRANT FROM THE INTERNATIONAL COMMITTEE FOR THE STUDY OF INFANTILE PARALYSIS ORGANIZED BY JEREMIAH MILBANK. Price, $6. Pp. 562. Baltimore: The Williams & Wilkins Company, 1932.

POSSIBILITIES AND NEED FOR DEVELOPMENT OF LEGAL MEDICINE IN THE UNITED STATES. WITH A SUPPLEMENT ON UNIVERSITY DEPARTMENTS IN THE FIELD OF CRIMINOLOGY. Bulletin No. 87. Prepared for the National Research Council Committee on Medicolegal Problems by Oscar T. Schultz. Price, $1.50. Pp. 135. Washington, D. C.: The National Research Council of the National Academy of Sciences, 1932.

SEKTIONSTECHNIK. Von Professor Dr. Robert Rössle, Direktor des Pathologischen Instituts der Universität Berlin. Price, 2.20 marks. Pp. 50, mit 7 Abbildungen. Berlin: Julius Springer, 1932.

FACIAL GROWTH IN CHILDREN WITH SPECIAL REFERENCE TO DENTITION. Part I by Corisande Smyth. Part II by Matthew Young. Medical Research Council Special Report Series No. 171. Price, 1s. 6d., net. Pp. 83. London: His Majesty's Stationery Office, 1932.

MEDICAL USES OF RADIUM: SUMMARY OF REPORTS FROM RESEARCH CENTRES FOR 1931. Medical Research Council Special Report Series No. 174. Price, 1s. 3d., net. Pp. 59. London: His Majesty's Stationery Office, 1932.

TENTH SCIENTIFIC REPORT ON THE INVESTIGATIONS OF THE IMPERIAL CANCER RESEARCH FUND. Under the direction of the Royal College of Surgeons of England. Published by the Authority of the Executive Committee. Price, 30s. Pp. 203, with 55 plates. London: Taylor and Francis, 1932.

TYPHO EXANTHEMATICO DE SAO PAULO. By José de Toledo Piza, J. R. Meyer and Luis Salles Gomes. Pp. 156, with 52 figures. Sao Paulo: Sociedade Impressora Paulista, 1932.

DER CORONARKREISLAUF PHYSIOLOGIE, PATHOLOGIE, THERAPIE. Von Dr. Max Hochrein, Professor an der Universität Leipzig. Pp. 227, mit 54 Abbildungen. Price, 24 marks. Berlin: Julius Springer, 1932.

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